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Demyelinating Risk with TNF Inhibitors versus Other Targeted DMARDs in Rheumatoid Arthritis: An emulated target trial using the French National Health Data System (DEMY-TNF)

Study Protocol

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1 - Objectives

1.1 – Principal Objective

To compare the risk of nervous system demyelinating events in patients with rheumatoid arthritis (RA) initiating TNF inhibitors versus CTLA4-Ig or IL-6 inhibitors as first-line biologic therapy after at least one conventional synthetic DMARD (csDMARD) (target trial emulation (TTE) 1: TNFi vs [CTLA4-Ig or IL-6i]).

1.2 – Secondary Objectives

To assess the risk of demyelinating events considering those affecting the central nervous system (CNS) and the peripheral nervous system (PNS) separately, in RA patients initiating treatment with TNF inhibitors versus CTLA4-Ig or IL-6 inhibitors, as first-line biologic therapy after csDMARD (TTE 1: TNFi vs [CTLA4-Ig or IL-6i]).

To compare the risk of nervous system demyelinating events in patients with RA initiating TNF inhibitors versus:

- CTLA4-Ig or IL-6 inhibitors or Janus kinase inhibitors (JAK inhibitors) (TTE 2: TNFi vs [CTLA4-Ig or IL-6i or JAKi])
- CTLA4-Ig (TTE 3: TNFi vs CTLA4-Ig)
- IL-6 inhibitors (TTE 4: TNFi vs IL-6i)
- JAK inhibitors (TTE 5: TNFi vs JAKi)

2 – Methods

2.1 – Study design

We will emulate target trials in RA patients initiating first-line biotherapies. First, we will design each of the target randomized controlled trial, i.e. the trials that would have been set up to answer the causal question, and second, we will emulate them as closely as possible by using observational data from the French National Health Data System (SNDS).

TTE 1: TNFi vs [CTLA4-Ig or IL-6i]:

Since treatments in the comparator group (IL-6 inhibitors and CTLA4-Ig) were prescribed as first-line therapies since 2014 (2013 EULAR and 2014 SFR recommendations), the inclusion period will start on Janurary 1, 2014 and end in December 31, 2024 to allow for one year of follow-up.

We will construct an active-comparator, new-user cohort study including all patients meeting eligibility criteria defined below.

We will report the target trials and their emulations the tables below and the appendices, in accordance with the TARGET guidelines.

Table 1. Components of the primary target trial and its emulation: TNFi vs [CTLA4-Ig + IL-6i]

	Target trial specification	Target trial emulation
Eligibility criteria	- Adults aged 18 or above - With RA - Treatment with at least one csDMARD in the six month before the index date - No prior use of any tDMARD (i.e. biologic, including anti-CD20 and JAKi) - No history of cancer in the 5 years before the index date - No history of demyelinating events - Prescription to initiate a tDMARD	Same as for target trial. RA and cancer history was identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary, related, or associated diagnoses).
Treatment strategies	(1) Initiation of TNFi therapy and continuation over follow-up until treatment discontinuation or switch to another tDMARD. (2) Initiation of CTLA4-Ig or IL-6 inhibitor therapy and continuation over follow-up until treatment discontinuation or switch to another tDMARD. When clinically warranted during the follow-up, patients and their physicians decide whether to start, stop or switch therapy. Concomitant csDMARD treatment are allowed.	Same as for the target trial Date of medication initiation is the first date of dispensing or in-hospital administration. We calculated discontinuation dates using the recommended dosing schedule of each drug. We considered treatment to be continuous if there was a gap of less than 90 days between successive prescriptions
Assignment to treatment strategies	Participants are randomly assigned to a strategy at inclusion. Participants and their treating physicians are aware of the assigned treatment strategy.	Individuals are assigned to the treatment strategies that their observed data are compatible with, i.e. according to the first tDMARD dispensed/administrated (ATC codes). We will emulation randomization using inverse probability weighting on a

		propensity score that uses baseline confounders.
Outcomes	Primary endpoint: cumulative incidence of demyelinating events of the nervous system. Secondary endpoints: - cumulative incidence of demyelinating events of the central nervous system (CNS) - cumulative incidence of demyelinating events of the peripheral nervous system (PNS)	Same as for the target trial Demyelinating events are identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary and related diagnoses)
Follow-up	Starts at baseline and ends at the first demyelinating event, death, administrative end of follow-up, treatment discontinuation, switch to another tDMARD, whichever happens first	Same as for the target trial A carry-over period of 3 months will be implemented in each treatment arm
Causal contrast	As-treated and ITT effect. The as-treated estimand addresses the treatment difference for all assigned patients while they remain on their assigned therapy, regardless of concomitant csDMARD use. The causal contrast will be quantified using a hazard ratio. The difference in cumulative incidence of the outcome at 10 years will be given for exploratory purposes.	Observational analog of the as-treated and ITT effect
Analysis	Cox model.	Weighted Cox model (IPTW on propensity score using covariates at index date)

For the TTE 2 to 5, only the comparator differs (and, where applicable, the non-eligibility criteria are adapted so that all patients can be eligible for all the strategies being compared). Complete specifications for these target trials and their emulation are available in the appendices.

2.2 – Study timelines

The inclusion period will extend from January 1, 2014 to December 31, 2024. The observation period will extend from January 1, 2014 to December 31, 2025, to allow for at least one year of follow-up; and

the data extraction period from January 1, 2006 to December 31, 2025, to allow for measurement of baseline covariates and a look-back period to exclude prevalent users of tDMARDs.

For TTE 2 and 5, since JAKi are prescribed as second line biotherapies in RA since 2017, the inclusion period will start on January 1, 2017.

2.3 – Data Sources

French National Health Data System (SNDS).

3 – Study population

3.1 – Source Population

The French population covered by the national health insurance system (all insurance schemes available in the SNDS), representing approximately 99% of the French population.

3.2 – Study population

3.2.1 – Inclusion criteria

The study population will be extracted from the source population (extraction period: January 1, 2006 to December 31, 2025). The following individuals will be included:

- Adult beneficiaries (aged $\geqslant$18 years): this choice is justified by the fact that the vast majority of rheumatoid arthritis (RA) cases occur in adulthood. Therefore, excluding the pediatric population—who are also difficult to identify in the SNDS—should not bias the results.

- Diagnosis of RA: identified using ICD-10 codes recorded before the index date, either in the long-term disease (ALD) registry or in the hospital discharge database (PMSI MCO; primary, related, or associated diagnoses). Previous studies have shown that RA can be reliably identified in the SNDS.

- History of treatment with at least one csDMARD: defined by at least one dispensing in the 6 month before the index date. This reflects current treatment guidelines, where targeted therapies are initiated after inadequate response to csDMARDs.

The index date is defined as the date of initiation of the first TNFi, CTLA4-Ig, or IL-6i.

3.2.2 – Non-inclusion criteria

- History of demyelinating events before baseline, identified using ICD-10 codes (ALD registry or PMSI MCO hospitalization).

- Prior exposure to any tDMARD (including JAKi and anti-CD20) before the index date.

- History of any tDMARD use during the look-back period (January 1, 2006 to January 1, 2014), to ensure inclusion of new users.

- History of cancer in the 5 years before the index date: identified using ICD-10 codes recorded before the index date, either in the long-term disease (ALD) registry or in the hospital discharge database (PMSI MCO; primary, related, or associated diagnoses). Previous studies have shown that cancer can be reliably identified in the SNDS.

3.3 – Disease of interest

The disease of interest is rheumatoid arthritis. It will be identified using long-term disease status (Affection de Longue Durée, ALD) with the corresponding ICD-10 codes recorded in the DCIR database, or from hospital data in the PMSI database (corresponding ICD-10 codes recorded as primary, related, or associated diagnoses in MCO hospitalizations).

RA will be identified using the ICD-10 codes listed below.

Table 1 : ICD-10 codes of interest and exclusion codes used for the identification of rheumatoid arthritis

Disease	**ICD-10 codes of interest**	**ICD-10 codes to exclude**
Rhumatoid Arthritis (RA)	**M05**, M050, M051, M052, M053, M058, M059 **M06**, M060, M062, M063, M064, M068, M069 M080	M061 (Still's disease)

3.4 – Definition of follow-up

Follow-up will begin at initiation of the first tDMARD (=index date) and continue until the occurrence of an endpoint, treatment discontinuation, switching of another tDMARD, death, or the end of the observation period (31/12/2025), whichever occurred first.

3.5 – Treatment of interest

We will consider the following treatment exposures (Table 2):

- « treatment arm» : TNF-inhibitors (TNFi)
- « comparator arm »:
    - Target trial TNFi vs [CTLA4-Ig or IL-6i]: anti-IL6R, CTLA4-Ig
    - Target trial TNFi vs [CTLA4-Ig or IL-6i or JAKi]: anti-IL6R, CTLA4-Ig, JAK inhibitors
    - Target trial TNFi vs CTLA4-Ig : CTLA4-Ig
    - Target trial TNFi vs IL-6i : IL-6i
    - Target trial TNFi vs JAKi : JAKi

ATC codes for medications dispensed in outpatient settings will be used to identify relevant exposures in the SNDS database, and UCD codes will be used to identify tDMARDs administered during hospitalizations.

*Table 2 : tDMARD (*originator products or biosimilars when available) *ATC, CIP13, and UCD codes*

tDMARD	**ATC codes**	**CIP13 codes**	**UCD codes**
anti-TNFα	L04AB01, L04AB02, L04AB04, L04AB05, L04AB06	3400930092675, 3400930044599, 3400930044605, 3400937719100, 3400930111017, 3400937719568, 3400939605227, 3400930098943, 3400930098950, 3400930098967, 3400930142288, 3400930141755, 3400930141809, 3400930141779, 3400930141762, 3400930126165, 3400930042687, 3400930042489, 3400930116494, 3400930116500, 3400930178805, 3400930155080, 3400930155097, 3400930143711, 3400930143728, 3400930144114, 3400930144121, 3400939732008, 3400930076286, 3400927568480, 3400927568312, 3400939730974, 3400939730745	9418787, 9398352, 9213737, 9402303, 9438896

anti-IL6R	L04AC07, L04AC14	3400927824845, 3400930145524, 3400930100608, 3400930100622, 3400930100615, 3400930100639	9331879, 9331885, 9331891, 9404377, 9443791
CTLA4-Ig	L04AA24	3400926884376, 3400930019207, 3400958098932	9300181, 9390267, 9411957, 9447808, 9447814
anti-JAK	L04AA29, L04AA37, L04AA44	3400930087367, 3400930087398, 3400930088111, 3400930159453, 3400930193983	

3.6 – Exposure periods of the treatments of interest

Two types of periods will be considered:

- The covered period, which begins on the date of the first dispensing and ends at the end of the period covered by the last dispensing (variable depending on the treatment considered; see Table 3). Any gap of ≤ 90 days between the end of exposure and a new dispensing will not be considered as treatment discontinuation. Likewise, a treatment sequence cannot be considered discontinued without at least 90 days of follow-up after the end of the period covered by a dispensing.

- The exposed period, which begins after a lag period following the start of the covered period and ends after a carry-over period following the end of the covered period. In this study, since demyelinating events may occur just after the first administration of treatment, the lag period will be set to zero in the main analysis. The carry-over period will be 3 months, in order to avoid missing potential delayed neurological effects of treatments (risk of protopathic bias if no carry-over period is applied).

A sensitivity analyses will be performed by varying the duration of the lag and carry-over periods:lag of 90 days and carry-over period of 180 days

Table 3: Duration of the coverage period following a medication dispensing, according to the treatment considered.

Treatment	Duration covered / delivery (days)
tDMARD	
Infliximab	60
Adalimumab	30
Certolizumab	30
Golimumab	30

Etanercept	30
Abatacept	30
Tocilizumab	30
Tofacitinib	30
Baricitinib	30
Filgotinib	30
Upadacitinib	30

3.7 – Other treatments considered in the study

The following treatments and codes to define exposure to csDMARDs (eligibility criteria) were used (Table 3) :

Table 3 : csDMARD ATC and CIP13 codes

Treatment	ATC codes	CIP13 codes
csDMARD		
Méthotrexate	L01BA01, L04AX03	3400930016343,3400938974041,3400930016367,3400930016381, 3400930016404, 3400930004319, 3400938984156, 3400930016428, 3400930016442, 3400930016466, 3400930016312, 3400930670682, 3400931602187, 3400931501251, 3400930020258, 3400926889050, 3400930020296, 3400930020326, 3400926774974, 3400930020364, 3400930020395, 3400926889401, 3400930020432, 3400930020463, 3400926889920, 3400930020494, 3400930020524, 3400926888688, 3400930020197, 3400930075012, 3400930075029, 3400930075036, 3400930075043, 3400930075067, 3400930075074, 3400930075081, 3400930075005, 3400930120200, 3400930120231, 3400930120842, 3400930120866, 3400930120880, 3400930120927, 3400930120187
Leflunomide	L04AA13	3400935417138, 3400935416476, 3400949506262, 3400949508792, 3400935416995, 3400949506033, 3400949508853, 3400949512065, 3400941701245, 3400941701306, 3400922084664, 3400922084893, 3400922084954, 3400922085265, 3400930172063, 3400930172070, 3400949726806, 3400949727056
Sulfasalazine	A07EC01	3400932268801
Hydroxychloroquine	P01BA02	3400930838198, 3400936441460
tDMARD		
anti-CD20	L01XC02	9197702, 9197719, 9403691, 9427450, 9427467, 9423831

Other treatments of interest will also be considered, either for adjustment, comparison between the study populations, or description of the study populations:

- Oral corticosteroids: reflecting the severity of rheumatoid arthritis (RA), ATC codes H02AB

- NSAIDs (non-steroidal anti-inflammatory drugs): which may also potentially reflect RA severity; ATC codes listed below (Table 5)

Table 5: ATC codes for NSAIDs.

Treatments of interest	**ATC codes**
AINS	M01AE09 M01AE11 M01AE01 M01AE02 M01AB01 M01AE03 M01AB05 M01AB16 M01AH01 M01AH05 M01AC01 M01AC02 M01AC06 M01AX01 M01AX17 M01AB08 M01AE16 M01AX02 M01AX22 M01AX21 M01BA

3.8 - Other diseases considred in the study

History of cancer :

Hisotry of cancer case was identified if, in the five years before index date, there was at least one hospital stay with an ICD-10 cancer code (C code) for the primary diagnosis, or at least one hospital stay with both a C code for a related diagnosis and a chemotherapy or radiotherapy code (Z511 or Z510, respectively) for the primary diagnosis. ICD-10 codes in the long-term disease registry were also considered to define history of cancer.

History of cardiovacular disease or venous thromboembolic events :

History of these events were considered when there was an hospital stay or long-term disease ICD-10 code of any of the following codes below, before index date :

Disease	**ICD-10 Codes**
Acute myocardial infarction (AMI)	I21, I22
Ischemic heart disease (chronic / angina)	I20, I25

Disease	ICD-10 Codes
Ischemic stroke	I63
Stroke (unspecified)	I64
Hemorrhagic stroke	I60, I61, I62
All stroke (composite)	I60–I64
Heart failure	I50
Cardiovascular mortality (broad definition)	I00–I99
Pulmonary embolism (PE)	I26
Deep vein thrombosis (DVT)	I80 (especially I80.1–I80.3), I82

History of diabetes :

History of diabetes will be defined as any hospital visit or a long-term disease benefit with a ICD-10 diagnostic code described in the table below, or a dispensing of a treatment described in the table below.

Disease / Category	ICD-10 Codes / Treatments
Type 1 diabetes	E10
Type 2 diabetes	E11
Other specified diabetes	E13
Unspecified diabetes	E14
All diabetes (composite)	E10–E14
Insulins	All insulin formulations (ATC: A10A)
Oral antidiabetic drugs (non-insulin)	ATC: A10B
Biguanides (e.g. metformin)	A10BA
Sulfonylureas	A10BB
DPP-4 inhibitors	A10BH
GLP-1 receptor agonists	A10BJ
SGLT2 inhibitors	A10BK
Other glucose-lowering drugs	A10BX

4 – Outcomes

4.1 – Primary outcome

Occurrence of a first ICD-10 code for a demyelinating event affecting the central nervous system (CNS) or the peripheral nervous system (PNS) after the index date.

Incident demyelinating events will be identified using ICD-10 codes from MCO hospitalizations (primary or related diagnosis: DP/DR) and long-term disease (ALD) records (Table 7).

Table 7: Demyelinating events of interest

Neurological event	**CNS or PNS**	**ICD-10 code**
Multiple sclerosis	CNS	G35
Other acute disseminated demyelinating diseases	CNS	G36
Neuromyelitis optica [Devic]	CNS	G360
Acute and subacute hemorrhagic leukoencephalitis [Hurst]	CNS	G361
Other specified acute disseminated demyelinating diseases	CNS	G368
Acute disseminated demyelinating disease, unspecified	CNS	G369
Other demyelinating diseases of the central nervous system	CNS	G37
Diffuse sclerosis	CNS	G370
Central demyelination of the corpus callosum	CNS	G371
Central pontine myelinolysis	CNS	G372
Acute transverse myelitis (in demyelinating diseases of the CNS)	CNS	G373
Subacute necrotizing myelitis	CNS	G374
Concentric sclerosis [Baló] (central nervous system)	CNS	G375
Other specified demyelinating diseases of the central nervous system	CNS	G378
Demyelinating disease of the central nervous system, unspecified	CNS	G379
Optic neuritis	CNS	H46
Inflammatory polyneuropathies	PNS	G61
Guillain–Barré syndrome	PNS	G610
Other inflammatory polyneuropathies	PNS	G618

4.2 – Secondary outcomes

The secondary outcomes will be the following:

- Occurrence of a first ICD-10 code for a demyelinating event affecting the central nervous system (CNS) after the index date: multiple sclerosis, neuromyelitis optica (Devic's disease), and other demyelinating disorders affecting the CNS (see Table 7).

- Occurrence of a first ICD-10 code for an incident demyelinating event affecting the peripheral nervous system (PNS) after the index date: Guillain–Barré syndrome and inflammatory polyneuropathies (see Table 7).

5 – Covariates

Covariates considered will be sex, age at index date, year of index date, Charlson's Comorbidity Index (version adapted to the SNDS), proxies for heavy tobacco or alcohol consumption, obesity, care consumption in the year before baseline (number of hospitalizations for RA), cumulative corticosteroids dose in the year before baseline, exposure to NSAIDs in the year before baseline, time between first csDMARD and baseline (categorized to account for prevalent csDMARD users), and full health expense coverage for low income.

6 – Statistical analyses

In these analyses, an "as-treated" approach will be used, in which only the periods during which the patient is exposed to the tDMARDs of interest will be considered.

In secondary analyses assessing the effects on central and peripheral demyelinating events separately, peripheral nervous system (PNS) events will be treated as competing events in the analysis of central nervous system (CNS) outcomes, and vice versa. Specifically, individuals experiencing a PNS event will be censored at the time of that event and will be considered as not having experienced the CNS outcome of interest (and conversely for CNS events in the analysis of PNS outcomes).

6.1 – Descriptive statistics

A description of patients exposed to the treatments of interest will be performed according to their exposure, based on the following variables:

- Age at the index date
- Sex
- Year of the index date
- Time between the first csDMARD prescription and the index date
- Type of csDMARD most recently dispensed before the index date
- Duration of follow-up (in years)
- Number and median time from index date of tDMARD discontinuations and switches during follow-up.
- Comorbidities: inflammatory bowel disease (IBD), sarcoidosis, lupus, thyroiditis, obesity, diabetes, hypertension, dyslipidemia, chronic kidney disease, chronic liver disease
- Proxy status for tobacco use

- Proxy status for alcohol consumption
- Low-income health coverage
- Charlson comorbidity score at the index date
- Hospitalization for rheumatoid arthritis in the year preceding the index date
- Whether dispended with at least one corticosteroids in the year preceding the index date
- Cumulative corticosteroid dose in the year preceding the index date
- At least one dispensing of NSAIDs in the year preceding the index date.

6.2 – Analytical statistical analysis

6.2.1 – Propensity score

The variables included in the propensity score are those described in the "covariates" section.

The propensity score will be estimated using a logistic regression model to calculate the probability of receiving TNFi vs comparator according to baseline covariates.

Patients will then be weighted using the IPTW (Inverse Probability of Treatment Weighting) method. The propensity distribution will be trimmed at the first and 99th percentiles and inversely transformed resulting in truncated stabilised weights.

6.2.2 – Quality of the weighting

To assess the quality of the matching, standardized mean differences between the two treatment groups will be calculated, and a love plot and histograms of the propensity score will be plotted. Differences less than 10% will indicate balance between treatments.

6.2.3 – Statistical estimator of the treatment effect

Hazard ratios (HRs) and 95% confidence intervals will be estimated using Cox proportional hazards models incorporating inverse probability of treatment weighting to estimate the average treatment effect (ATE) in the target population. For exploratory purposes, absolute risks and risk differences at 10 years will be derived from Kaplan-Meier estimates for the primary endpoint.

6.2.4 – Sensitivity analyses

These prespecified sensitivity analyses will be conducted :

- Variation of carry-over durations (L0R0, L0R180)
- Non-inclusion of patients treated with leflunomide in the siw month before the index date.Time-dependent IPCW weighting for treatment nonadherence, intercurrent events

(death, introduction of concomitant treatments, demyelinating events in the secondary analysis).

- MNAR pattern-mixture analysis to control for nonadherence, intercurrent events (death, introduction of concomitant treatments, demyelinating events in the secondary analysis). It is assumed that, given equal measured covariates, censored patients would have had a different risk of the outcome if they had remained on treatment. This risk of the outcome in the TNFi will be varied until no statistically significant difference is observed. Had a deleterious effect of TNFi treatment persisted up to a hypothetical 50% decrease in post-discontinuation risk of the outcome, it would suggest moderate robustness to a violation of the MAR assumption.

7 – Appendix

7.1 – Secondary target trial emulations

eTable 1. Components of the target trial and its emulation for the secondary target trial emulation: CNS and PND analyzed separately. Modifications to the primary target trial are highlighted in bold.

	Target trial specification	Target trial specification
Eligibility criteria	- Adults aged 18 or above - A diagnosis of RA - Treatment with a csDMARD in the six month before index date. - No prior use of any tDMARD (including anti-CD20) - No history of cancer in the 5 years before the index date - No history of demyelinating events Baseline will be defined as the date of the first dispensing of either of the drugs under comparison.	Same as for target trial. RA was identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary, related, or associated diagnoses)
Treatment strategies	1) Initiation of TNFi therapy at baseline and continuation over follow-up until treatment discontinuation or switch to another tDMARD.	Same as for the target trial We defined the date of medication initiation to be the first date of a prescription. We calculated discontinuation dates using the recommended dosing schedule of each drug. We considered treatment to be

	2) Initiation of CTLA4-Ig or IL-6 inhibitor therapy at baseline and continuation over follow-up until treatment discontinuation or switch to another tDMARD. When clinically warranted during the follow-up, patients and their physicians decide whether to start, stop or switch therapy. Background csDMARD treatment was allowed.	continuous if there was a gap of less than 90 days between successive prescriptions
Assignment to treatment strategies	Participants are randomly assigned to a strategy at baseline. Participants and their treating physicians are aware of the assigned treatment strategy.	Participants are classified at baseline according to the tDMARD initially prescribed. Randomization is emulated by inverse probability weighting on a propensity score that uses baseline confounders.
Outcomes	Cumulative incidence of a **central nervous system (CNS) demyelinating event, or peripheral nervous system (PNS) demyelinating event, analysed separately**.	Same as for the target trial Demyelinating events are identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary and related diagnoses)
Follow-up	Starts at baseline and ends at the first demyelinating event **(the other location analyzed as a competitive event)**, death, administrative end of follow-up, treatment discontinuation, switch to another tDMARD whichever happens first	Same as for the target trial A carry-over period of 3 months will be implemented in each treatment arm
Causal contrast	As-treated and ITT effect The causal contrast will be quantified using a hazard ratio. The difference in cumulative incidence of the outcome at 10 years will be given for exploratory purposes.	Observational analog of the as-treated and ITT effect
Analysis	Cumulative incidence curves. Cox model.	Weighted cumulative incidence curves. Weighted Cox model (IPTW on propensity score using baseline covariates)

eTable 2. Components of the TTE 2 and its emulation: TNFi vs [CTLA4-Ig + IL-6i +JAKi]

	Target trial specification	Target trial specification
Eligibility criteria	- **Adults aged between 18 and 65** - A diagnosis of RA - Treatment with a csDMARD - No prior use of any tDMARD (including anti-CD20) - No history of cancer in the 5 years before the index date - **No history of cardiovascular disease or venous thromboembolic events** - **No history of heavy tobacco use** - **No history of severe obesity** - **No history of diabetes** - No history of demyelinating events Baseline will be defined as the date of the first dispensing of either of the drugs under comparison.	Same as for target trial. RA was identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary, related, or associated diagnoses)
Treatment strategies	1) Initiation of TNFi therapy at baseline and continuation over follow-up until treatment discontinuation or switch to another tDMARD. 2) Initiation of CTLA4-Ig or IL-6 inhibitor **or JAKi** therapy at baseline and continuation over follow-up until treatment discontinuation or switch to another tDMARD. When clinically warranted during the follow-up, patients and their physicians decide whether to start, stop or switch therapy.	Same as for the target trial We defined the date of medication initiation to be the first date of a prescription. We calculated discontinuation dates using the recommended dosing schedule of each drug. We considered treatment to be continuous if there was a gap of less than 90 days between successive prescriptions

	Background csDMARD treatment was allowed. **Inclusion period will start in January 1, 2017**.	
Assignment to treatment strategies	Participants are randomly assigned to a strategy at baseline. Participants and their treating physicians are aware of the assigned treatment strategy.	Participants are classified at baseline according to the tDMARD initially prescribed. Randomization is emulated by inverse probability weighting on a propensity score that uses baseline confounders.
Outcomes	Cumulative incidence of demyelinating events of the nervous system.	Same as for the target trial Demyelinating events are identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary and related diagnoses)
Follow-up	Starts at baseline and ends at the first demyelinating event, death, administrative end of follow-up, treatment discontinuation, switch to another tDMARD, whichever happens first	Same as for the target trial A carry-over period of 3 months will be implemented in each treatment arm
Causal contrast	Per-protocol effect The causal contrast will be quantified using a hazard ratio. The difference in cumulative incidence of the outcome at 10 years will be given for exploratory purposes.	Observational analog of the per-protocol effect
Analysis	Cumulative incidence curves. Cox model.	Weighted cumulative incidence curves. Weighted Cox model (IPTW on propensity score using baseline covariates)

eTable 3. Components of the TTE 3 and its emulation: TNFi vs [CTLA4-Ig]

	Target trial specification	Target trial specification
Eligibility criteria	- Adults aged 18 or above - A diagnosis of RA - Treatment with a csDMARD in the 6 month before index date - No history of cancer in the 5 years before index date - No prior use of any tDMARD (including	Same as for target trial. RA was identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary, related, or associated diagnoses)

	anti-CD20, JAKi, **and IL-6i**) - No history of demyelinating events Baseline will be defined as the date of the first dispensing of either of the drugs under comparison.	
Treatment strategies	1) Initiation of TNFi therapy at baseline and continuation over follow-up until treatment discontinuation or switch to another tDMARD. 2) Initiation of **CTLA4-Ig** therapy at baseline and continuation over follow-up until treatment discontinuation or switch to another tDMARD. When clinically warranted during the follow-up, patients and their physicians decide whether to start, stop or switch therapy. Background csDMARD treatment was allowed.	Same as for the target trial We defined the date of medication initiation to be the first date of a prescription. We calculated discontinuation dates using the recommended dosing schedule of each drug. We considered treatment to be continuous if there was a gap of less than 90 days between successive prescriptions
Assignment to treatment strategies	Participants are randomly assigned to a strategy at baseline. Participants and their treating physicians are aware of the assigned treatment strategy.	Participants are classified at baseline according to the tDMARD initially prescribed. Randomization is emulated by inverse probability weighting on a propensity score that uses baseline confounders.
Outcomes	Cumulative incidence of demyelinating events of the nervous system.	Same as for the target trial Demyelinating events are identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary and related diagnoses)
Follow-up	Starts at baseline and ends at the first demyelinating event, death, administrative end of follow-up, treatment discontinuation, switch to	Same as for the target trial A carry-over period of 3 months will be implemented in each treatment arm

	another tDMARD, whichever happens first	
Causal contrast	Per-protocol effect The causal contrast will be quantified using a hazard ratio. The difference in cumulative incidence of the outcome at 10 years will be given for exploratory purposes.	Observational analog of the per-protocol effect
Analysis	Cumulative incidence curves. Cox model.	Weighted cumulative incidence curves. Weighted Cox model (IPTW on propensity score using baseline covariates)

eTable 4. Components of the TTE 4 and its emulation: TNFi vs [IL-6i]

	Target trial specification	Target trial specification
Eligibility criteria	- Adults aged 18 or above - A diagnosis of RA - Treatment with a csDMARD in the 6 month before index date - No history of cancer in the 5 years before index date - At least one year of potential follow-up - No prior use of any tDMARD (including anti-CD20, JAKi, **CTLA4-Ig**) - No history of demyelinating events Baseline will be defined as the date of the first dispensing of either of the drugs under comparison.	Same as for target trial. RA was identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary, related, or associated diagnoses)
Treatment strategies	1) Initiation of TNFi therapy at baseline and continuation over follow-up until treatment discontinuation or switch to another tDMARD. 2) Initiation of **IL-6i** therapy at baseline and continuation over	Same as for the target trial We defined the date of medication initiation to be the first date of a prescription. We calculated discontinuation dates using the recommended dosing schedule of each drug. We considered treatment to be continuous if there was a gap of less than 90 days between successive prescriptions

	follow-up until treatment discontinuation or switch to another tDMARD. When clinically warranted during the follow-up, patients and their physicians decide whether to start, stop or switch therapy. Background csDMARD treatment was allowed.	
Assignment to treatment strategies	Participants are randomly assigned to a strategy at baseline. Participants and their treating physicians are aware of the assigned treatment strategy.	Participants are classified at baseline according to the tDMARD initially prescribed. Randomization is emulated by inverse probability weighting on a propensity score that uses baseline confounders.
Outcomes	Cumulative incidence of demyelinating events of the nervous system.	Same as for the target trial Demyelinating events are identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary and related diagnoses)
Follow-up	Starts at baseline and ends at the first demyelinating event, death, administrative end of follow-up, treatment discontinuation, switch to another tDMARD, whichever happens first	Same as for the target trial A carry-over period of 3 months will be implemented in each treatment arm
Causal contrast	Per-protocol effect The causal contrast will be quantified using a hazard ratio. The difference in cumulative incidence of the outcome at 10 years will be given for exploratory purposes.	Observational analog of the per-protocol effect
Analysis	Cumulative incidence curves. Cox model.	Weighted cumulative incidence curves. Weighted Cox model (IPTW on propensity score using baseline covariates)

eTable 5. Components of the TTE 5 and its emulation: TNFi vs [JAKi]

	Target trial specification	Target trial specification
Eligibility criteria	- **Adults aged between 18 and 65**	Same as for target trial.

	- A diagnosis of RA - Treatment with a csDMARD - At least one year of potential follow-up - No prior use of any tDMARD (including anti-CD20) - No history of cancer in the 5 years before the index date - **No history of cardiovascular disease or venous thromboembolic events** - **No history of heavy tobacco use** - **No history of severe obesity** - **No history of diabetes** - No history of demyelinating events Baseline will be defined as the date of the first dispensing of either of the drugs under comparison.	RA was identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary, related, or associated diagnoses)
Treatment strategies	1) Initiation of TNFi therapy at baseline and continuation over follow-up until treatment discontinuation or switch to another tDMARD. 2) Initiation of **JAKi** therapy at baseline and continuation over follow-up until treatment discontinuation or switch to another tDMARD. When clinically warranted during the follow-up, patients and their physicians decide whether to start, stop or switch therapy. Background csDMARD treatment was allowed. **Inclusion period will start in January 1, 2017.**	Same as for the target trial We defined the date of medication initiation to be the first date of a prescription. We calculated discontinuation dates using the recommended dosing schedule of each drug. We considered treatment to be continuous if there was a gap of less than 90 days between successive prescriptions

Assignment to treatment strategies	Participants are randomly assigned to a strategy at baseline. Participants and their treating physicians are aware of the assigned treatment strategy.	Participants are classified at baseline according to the tDMARD initially prescribed. Randomization is emulated by inverse probability weighting on a propensity score that uses baseline confounders.
Outcomes	Cumulative incidence of demyelinating events of the nervous system.	Same as for the target trial Demyelinating events are identified using ICD-10 codes recorded in i) long-term disease registries or ii) hospital stays (primary and related diagnoses)
Follow-up	Starts at baseline and ends at the first demyelinating event, death, administrative end of follow-up, treatment discontinuation, switch to another tDMARD, whichever happens first	Same as for the target trial A carry-over period of 3 months will be implemented in each treatment arm
Causal contrast	Per-protocol effect The causal contrast will be quantified using a hazard ratio. The difference in cumulative incidence of the outcome at 10 years will be given for exploratory purposes.	Observational analog of the per-protocol effect
Analysis	Cumulative incidence curves. Cox model.	Weighted cumulative incidence curves. Weighted Cox model (IPTW on propensity score using baseline covariates)