

## Study Protocol: Comparative Effectiveness and Safety of Biosimilar and Legacy Drugs

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<b>Version</b>	1.0
<b>Date</b>	October 24, 2018
<b>Research question:</b> What is the comparative effectiveness and safety of biosimilar drugs versus their equivalent legacy drugs?	
<p><b>Primary aims:</b></p> <p><b>To compare, in biologic-naïve patients who are new users of biosimilar drugs versus their equivalent legacy drugs:</b></p> <ol style="list-style-type: none"> <li>1. Frequency of discontinuation of the initial therapy</li> <li>2. Persistence on the initial therapy (time until drug discontinuation)</li> <li>3. Frequency of patients starting or increasing prednisone or other immunosuppressive drugs</li> <li>4. Frequency of and time to discontinuation of treatment due to ineffectiveness</li> <li>5. Frequency of and time to clinical remission/induction of response</li> <li>6. Frequency of and time to serious adverse events</li> </ol> <p><b>Secondary aims</b></p> <p><b>To describe in biologic-naïve patients who are new users of biosimilar drugs or their equivalent legacy drugs:</b></p> <ol style="list-style-type: none"> <li>1. Change in disease activity over time</li> <li>2. The frequency of, and time to, long-term outcomes (sustained remission, erosions in RA, radiographic progression in AS, and endoscopic mucosal healing scores in CD and UC).</li> <li>3. Change in quality of life measures over time</li> </ol> <p><b>Exploratory aims:</b></p> <ol style="list-style-type: none"> <li>1. To describe the above outcomes in patients switching from the legacy drug, to the biosimilar.</li> <li>2. To describe the above outcomes in patients switching from the biosimilar to the legacy drug.</li> </ol>	
<b>Study design</b>	Prospective and retrospective cohort
<b>Conditions</b>	Inflammatory rheumatic diseases- Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) Inflammatory Bowel Diseases (IBD) - Crohn's disease (CD) and Ulcerative Colitis (UC)

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<b>Study population</b>	Adult patients (18 years and older) from both sexes, in one of the conditions listed above, treated with biosimilar or its equivalent legacy drugs.
<b>Estimated enrolment start date</b>	October 2018
<b>Estimated enrolment end date</b>	March 2021
<b>Follow-up time</b>	Minimum 2 years (maximum 4.5)
<b>Estimated study completion date</b>	December 2022
<b>Exposure groups</b>	Biosimilar – exposed group Legacy drug – reference group
<b>Specific Outcomes</b>	
<ol style="list-style-type: none"> <li>1. Discontinuation of initial therapy, measured as the number of patients who discontinued their initial treatment during the follow-up period.</li> <li>2. Persistence on the initial therapy, defined as the time in months from cohort entry until drug discontinuation/switching.</li> <li>3. Frequency of patients starting or increasing prednisone or other immunosuppressive drug.</li> <li>4. Frequency of treatment failure, measured as the proportion of biosimilar or legacy drug patients who discontinue treatment due to ineffectiveness during follow-up.</li> <li>5. Time to treatment failure, measured in months from drug initiation until treatment failure.</li> <li>6. Frequency of clinical remission, measured by disease-specific measures including for RA, the Disease Activity Score (DAS28), and Simple Disease Activity Index (SDAI); the Spondylitis Disease Activity Score (ASDAS), the Assessment in SpondyloArthritis International Society (ASAS) response criteria, Bath Ankylosing Spondylitis Functional Index (BASFI), Stoke Ankylosing Spondylitis Spine Score (mSASSS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in AS; Crohn’s Disease Activity Index (CDAI), Harvey-Bradshaw Index (HBI) for CD and Mayo or Partial Mayo Score (PMS) for UC.</li> <li>7. Serious adverse events (SAEs), measured as the proportion of patients in each group presenting with an AE that is fatal or life-threatening, requiring or extending a patient’s hospitalization, resulting in persistent or significant disability or incapacity, inducing a congenital anomaly or birth defect, or otherwise be considered important by the physician.</li> <li>8. Long-term outcomes: frequency of sustained remission, presence of erosions in RA and radiographic progression in AS, and improvement or normalization of C-reactive protein and fecal calprotectin.</li> <li>9. Patient-reported change over time in the EuroQol-5D (EQ-5D), the Health Assessment Questionnaire Disability Index (HAQ-DI), the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), Visual Analogue Scale (VAS) and the veterans RAND 12 (VR-12).</li> </ol>	

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### List of abbreviations and definitions of terms

Abbreviation/Acronym	Definition
AE	Adverse event
AS	Ankylosing spondylitis
ASAS	Assessment in SpondyloArthritis International Society
ASDAS	Spondylitis Disease Activity Score
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BMI	Body Mass Index
CAN-AIM	CANadian Network for Advanced Interdisciplinary Methods for comparative effectiveness research
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CMD	Common data model
COXIBs	Cyclo-oxygenase-II inhibitors
CRF	Case report form
DAS28	Disease Activity Score with a 28-joint count
DAS28-CRP	DAS28 using the C-reactive protein level
DAS28-ESR	DAS28 using the erythrocyte sedimentation rate
DMARD	Disease-modifying antirheumatic drugs
EQ-5D	EuroQol-5D
HAQ-DI	Health Assessment Questionnaire Disability Index
HBI	Harvey-Bradshaw Index
IBD	Inflammatory Bowel Disease
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
ICF	Informed consent form
mSASSS	Stoke Ankylosing Spondylitis Spine Score
NPDUIS	National Prescription Drug Utilization Information System
NSAIDs	Non-steroidal anti-inflammatory drugs
PMS	Partial Mayo Score
RA	Rheumatoid Arthritis
SDAI	Simple Disease Activity Index

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VAS	Visual Analog Scale
VR-12	The veterans RAND 12-item health survey
UC	Ulcerative Colitis

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## A. BACKGROUND

In Canada, and worldwide, there is a need for updated, independent, real-world comparative effectiveness and safety data related to biologic drugs including biosimilar drugs. Biosimilar drugs hold the potential to improve access to needed therapies at a reduced cost, enabling savings to be reallocated to other needs, benefiting a broader population and improving overall health outcomes. However, updated, real-world evidence on the comparative effectiveness and safety of biosimilar drugs is lacking. Our CAN-AIM (Canadian Network for Advanced Interdisciplinary Methods for comparative effectiveness research) team is well-positioned to develop an effective program of research and surveillance related to biologic and biosimilar drugs.

With this proof of concept project, we aim to demonstrate the feasibility of creating a network of clinical cohorts and other resources to provide real-world information on the use of biosimilar drugs in Canada.

The core of our proposal revolves around the clinical datasets, but we will complement that with other data sources. To set the stage for our analyses, we will review data from the National Prescription Drug Utilization Information System (NPDUIS), a database that contains prescription claims-level data collected from publicly financed drug benefit programs in different provinces, to conduct an environmental scan of the use of biosimilars and their respective legacy drugs, and other anti-Tumor Necrosis Factor (TNF) agents covered by provincial drug plans from 2014-2017. Through this exercise, we aim to analyze, retrospectively, persistence and time to discontinuation over a 365-day period of biosimilars, their respective legacy drugs and other TNF inhibitors prescribed across Canada to establish existing patterns of drug use, as of 2017. This initial analysis will help us to confirm that currently, the use of biosimilars is lower than their legacy drugs<sup>1</sup>. Emerging regulatory reform to facilitate biosimilar use may change patterns of use, but much can be learnt from this initial review. The same analyses can be performed in the later part of our work (using NPDUIS data from 2018-2022) to again capture Canada-wide patterns and trends, and compare to the patterns of use prior to 2018. We will also conduct retrospective analyses of biosimilar use in our study cohorts.

## B. OBJECTIVES

**Our primary objectives are to compare, in biologic-naïve patients who are new users of biosimilar drugs versus their equivalent legacy drugs:**

1. Frequency of discontinuation of the initial therapy
2. Persistence (time until drug discontinuation) for the initial therapy
3. Frequency of patients starting or increasing prednisone or other immunosuppressive drugs
4. Frequency of and time to discontinuation of treatment due to ineffectiveness

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<sup>1</sup> Market Intelligence Report: Biologic Response Modifier Agents, 2015. [http://www.pmprb-cepmb.gc.ca/CMFiles/NPDUIS/PMBRB\\_16-240\\_MarketIntelligenceReport\\_E.pdf](http://www.pmprb-cepmb.gc.ca/CMFiles/NPDUIS/PMBRB_16-240_MarketIntelligenceReport_E.pdf)

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5. Frequency of and time to

- a. Induction and maintenance of response
- b. Clinical remission and sustained clinical remission

6. Frequency of and time to serious adverse events.

### C. METHODS

We will be working with two types of cohorts; more specifically, new cohorts collecting data prospectively and established cohorts that will share their retrospective and prospective data as per Data Transfer Agreements. Data from these cohorts will be analyzed together.

#### *Enrolment*

We are working with pan-Canadian, prospective cohorts of patients with inflammatory rheumatic diseases (rheumatoid arthritis, RA, and ankylosing spondylitis, AS) and Inflammatory Bowel Disease (IBD) (Crohn's disease, CD, and Ulcerative Colitis, UC). Cohort members eligible for our study are patients starting treatment with any biosimilar or any legacy drug. Patients will be enrolled over an approximate 24 month-period and the follow-up period will be up to four and a half years. A brief description of these cohorts is presented in Appendix A.

#### *Inclusion/exclusion criteria*

Our study will include cohort members from both sexes, 18 years and older, with a clinical diagnosis of inflammatory rheumatic disease (either RA or AS), or IBD (CD or UC) who have given their informed consent. There are no disease activity criteria for entry. At the time of enrolment in our study, patients in each disease group will be classified into the following treatment subgroups:

- Biologic-naïve, starting any biosimilar or its equivalent legacy drug;
- Patients switching to biosimilar or its equivalent legacy drug from an alternative biologic therapy;
- Patients switching to a biosimilar (or starting a new cycle with its equivalent legacy drug) who have successfully completed and exited a previous course of therapy with the equivalent legacy drug.

Our primary analyses will be on biologic-naïve patients but we will collect data on all three of the above subgroups for exploratory descriptive analyses.

#### *Follow-up*

Patients will be followed for a maximum period of four and a half years for our study including patients who permanently discontinue the biosimilar or its equivalent legacy drug treatment. Data for the study will be entered at enrolment and then approximately every 3 months in the first year of follow-up and then every 6 months thereafter up to 24 months (see Appendix B). To complement information collected by each cohort, patients' data obtained from administrative health databases, including hospitalizations, physician billing, and prescription drugs will also be collected. For those patients who reach the 24-month mark before the end of our study (Dec. 2022), we will continue to collect data at yearly intervals (with a final data collection at month 54) so that an exploratory analysis of outcomes beyond 24 months can be done. Off protocol

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visits for patient reported increases in disease activity will occur as clinically indicated, but no additional data are required for collection.

### *Variables*

The core of our clinical data resource is a set of established cohorts of selected conditions. Each cohort will contribute a minimal core set of variables (see below).

#### Variables collected at enrolment visit (baseline)

- Date of Birth (DOB)
- Sex
- Race/Ethnicity
- Education
- Height and weight (BMI)
- Smoking (Ever/Never, Current, pack-years)
- Major comorbidities (congestive heart failure, diabetes, hypertension, coronary artery disease, malignancy, renal failure, other)
- Use of physician services and hospitalizations in the year prior to baseline (including total physician use but also detailing specialty services)
- Relevant surgical history since disease onset (related to IBD or rheumatic condition, as is relevant).
- Disease diagnosis and duration
- Disease Phenotype by Montreal Classification System
- Past use of medication: steroids, non-biologic and biologic DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase-II inhibitors (COXIBs)

#### Variables collected at baseline visit and during follow-up visits

- Updated demographics (weight, smoking status, education, comorbidities)
- Clinical evaluation of disease activity and response: DAS-28 (Disease Activity Score with a 28-joint count), SDAI (Simple Disease Activity Index), ASAS (Assessment in SpondyloArthritis International Society) response criteria, ASDAS (Spondylitis Disease Activity Score), BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), BASFI (Bath Ankylosing Spondylitis Functional Index), mSASSS (Stoke Ankylosing Spondylitis Spine Score), physician's global assessment of disease activity (VAS 100 mm), Harvey-Bradshaw Index (HBI), Partial Mayo score (PMS), Crohn's Disease Activity Index (CDAI)
- Any patient reported outcomes: EQ-5D, HAQ-DI, SIBDQ, VR-12, patient's global assessment of disease activity (VAS 100 mm)
- Tender and swollen joint count (0–28) for RA and AS
- Reports from any endoscopic assessment done for clinical reasons (i.e. the endoscopy most proximal to the enrolment date and post proximal to annual follow-up visits, if available) with Mayo Endoscopic Score if available
- Reports from any cross-sectional imaging reports done before enrolment and between follow-up visits
- Complete blood count (CBC), creatinine, urinalysis (if available), ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), fecal calprotectin (if available), drug levels

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- Use of medication: steroids, non-biologic and biologic DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase-II inhibitors (COXIBs), budesonide, 5-aminosalicylates (oral and rectal)
- Data on therapy drug monitoring (if available): any measurements of medication concentration in blood (for biologic/biosimilar)
- Reason for discontinuation/switching medications, recorded by the physician at follow-up visits
- Occurrence of AEs and serious AEs (see below for details)
- Use of healthcare services between follow-up visits, such as physician visits and hospitalization data with details on primary and non-primary admission diagnoses and length of stay

### *Effectiveness Outcomes*

In each of the four conditions (RA, AS, CD, UC), the primary outcome will be persistence on treatment, measured as time from cohort entry until the occurrence of the first discontinuation. This of course is not a pure measure of effectiveness but rather combines elements of both safety and effectiveness (since patients discontinue for both reasons).

Additional primary effectiveness outcomes will be clinical remission, improvement, or induction of response, as outlined in Table 1. Secondary outcomes include sustained remission/maintenance of response (also included in Table 1). The measures of remission/improvement/induction of response include:

- For RA, DAS28-CRP or DAS28-ESR, and SDAI
- For AS, ASAS20 Response Criteria and ASDAS
- For CD, CDAI and HBI
- For UC, Mayo Score

Table 1 – Definitions for clinical outcomes

<b>Outcome</b>	<b>Condition</b>	<b>Definition</b>
Remission or low disease activity (LDA)	RA	Remission: DAS28-CRP<2.4, DAS28-ESR<2.6 and SDAI≤3.3 LDA: DAS28-CRP ≤2.9, DAS28-ESR ≤3.2 and SDAI ≤11.0
Disease improvement	AS	ASAS Response Criteria (ASAS 20): improvement of at least 20% in three of the four ASAS domain in comparison with the previous measurement.
Sustained remission	RA	Remission, using the previous definitions, for minimum of 12 months
	AS	Remission, defined as ASDAS <1.3, for minimum of 12 months
Induction of response	UC	Decrease by at least 3 points and/or 30% from baseline in the PMS with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1 within 3 months of initiation of

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		treatment
Maintenance of response	UC	Response, as defined above, in two consecutive visits (minimum of 3month-interval)
Clinical remission	UC	PMS $\leq 2$ , with no sub score $>1$ , assessed at 3, 6, and 9, and 12 months after initiation of treatment, and yearly follow-ups
Sustained clinical remission	UC	Clinical remission, as defined above, in two consecutive visits (minimum of 3-month interval)
Induction of response	CD	<u>Reduction in the HBI score of at least three points</u> at 3 months after treatment initiation.
Maintenance of response	CD	Response, as defined above, in two consecutive visits (minimum of 3 month interval)
Clinical remission	CD	HBI $\leq$ , assessed at 3, 6, 9, 12 and 18 months after initiation of treatment, and at yearly follow-ups thereafter, and CDAI $< 150$ assessed at 12 months
Sustained clinical remission	CD	Clinical remission, as defined above, in two consecutive visits (minimum of 3-month interval).
Loss of response	UC, CD	Failure to maintain response as per above definitions

### Secondary outcomes

Our secondary effectiveness outcomes include frequency of and time to treatment failure, defined as the proportion of patients in each group who discontinued treatment due to ineffectiveness, and as the time, in months, from cohort entry until treatment failure. We will also measure long-term outcomes, including the frequency of and time to sustained remission/maintenance of response (as outlined in Table 1), need for surgery, presence of erosions in RA and radiographic progression in AS, improvement or normalization of C-reactive protein and fecal calprotectin in CD and UC.

Additional secondary outcomes are: i) use of key medications, measured as the frequency of patients starting or changing dose of corticosteroids or non-biologic and biologic DMARDs drugs during follow-up; ii) rates of treatment failure, measured as the proportion of patients in each group who discontinued treatment due to ineffectiveness during follow-up; and iii) patient-reported outcomes, measured as changes over time in the EQ-5D, HAQ-DI, SIBDQ, VAS and VR-12.

### Safety outcomes: Adverse Events (AEs) and Serious AEs (SAEs)

Adverse events (AEs) will be assessed by the treating physician, who will judge the relationship between the study drug and the AE. SAEs (our primary outcome for safety) will be defined as an AE that is fatal or life-threatening, requiring or extending a patient's hospitalization, resulting in persistent or significant disability or incapacity, inducing a congenital anomaly or birth defect, or otherwise be considered important medical event by the physician. All deaths will be reported whether they were treatment-related or not. Adverse events of special interest for this study include infection (tuberculosis, fungal and other opportunistic infections, hepatitis B reactivation,



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and infections requiring hospitalization, an emergency room visit, or intravenous antibiotics) serious infusion reactions, cytopenias (i.e. leukopenia, drug-related anemia), new-onset congestive heart failure, malignancies, and demyelinating disorders.

### *Statistical analysis*

As mentioned earlier, our primary analyses will focus on patients who are biologic-naïve prior to starting one of the drugs under study. Secondary analyses of non-biologic naïve patients will be done, adjusting for number of prior biologics at baseline.

Baseline characteristics will be presented using descriptive statistics to compare the two treatment groups. All continuous data will be expressed as the median (with range or interquartile range, IQR) or mean (with standard deviation SD) when appropriate. Categorical data will be presented as counts and percentages. Further descriptive comparisons of follow-up data will include: mean and cumulative doses, augmentation/reduction of therapy, and initiation or changes in the dose of prednisone and DMARDs/immunosuppressive agents.

In univariate analysis, groups will be compared in terms of frequency of treatment discontinuation for any reason, treatment failure due to ineffectiveness, and the occurrence of AEs including SAEs. Clinical remission, disease progression, and patient-reported outcomes will be assessed at time points during follow-up. Disease damage will be assessed through presence of erosions/radiographic progression in RA and AS, and specific surgeries (joint replacements in AS and RA, abdominal surgery for CD and UC).

For the continuous variables, the change over time between the two groups will be analysed using linear mixed models for repeated measures. Fixed effects of time will be estimated, and diagnosis, sex and age will be included in the analysis as possible effect modifiers.

Kaplan–Meier curves will be used to compare time from cohort entry to: i) treatment discontinuation/switching for any reason, ii) treatment failure due to ineffectiveness; iii) first episode of clinical remission, iv) SAE v) disability. Additional Kaplan-Meier curves will be plotted to compare time under sustained remission (from first remission until loss of effectiveness).

Then the same outcomes will be assessed using multivariate survival analyses during follow-up. In these analyses, the main exposure will be modeled as binary time-fixed indicator of drug used at cohort entry, as well as time-dependent cumulative duration and time-dependent cumulative dose of the biosimilar and the legacy drug. Survival analysis (Cox regression model) will be conducted to evaluate the risk of any SAE during follow-up. Separate Cox regression analysis will be conducted to evaluate the risk serious infection (defined as those requiring a hospitalization, emergency visit, or intravenous antibiotics), malignancies, and congestive heart failure, during the observational period. All models (for effectiveness and safety analyses) will be adjusted for the baseline covariates: sex, age, race/ethnicity, education, smoking, comorbidities, disease duration, disease activity, non-biologic or biologic DMARDs drugs, steroids, NSAIDs and COXIBs.

### **D. CONFIDENTIALITY**

Any data collected from a participant is considered personal information and will be kept confidential in the limits of the Law. When scientific communications are published and

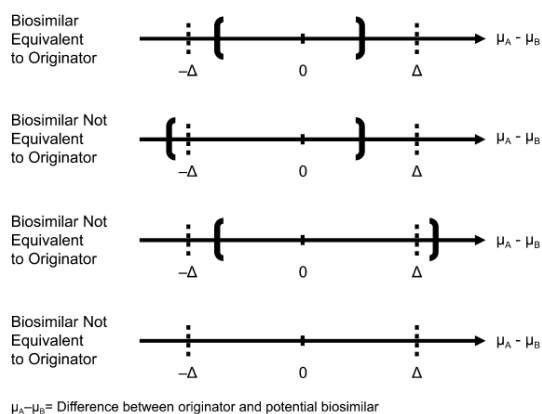
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disseminated on research conducted using the data, participants will not be identified or identifiable.

Data will be stored on secured servers at the Research Institute of the McGill University Health Centre (RIMUHC). All measures to respect the safety and confidentiality of data will be in place. Access to the servers will be limited to the study doctor, the principal investigator, and other members of the research team. Data for the study will be entered directly by the site using REDCap, a secure web application for building and managing databases. Sites unable to enter data into REDCap directly or sites transmitting retrospective and/or prospective data will send the anonymized, denormalized data to the lead site for analysis as per data transfer agreements.

### E. SAMPLE SIZE AND POWER ESTIMATION

The focus of our analysis is to demonstrate clinical and safety equivalence between the biosimilar and the legacy drug. An equivalence design in which results observed with a biosimilar product are within a pre-established range in relation to those obtained with the legacy drug (Figure 2) is recommended by both FDA<sup>2</sup> and the EMA<sup>3</sup> to establish similarity in clinical effects for the biosimilar product versus the legacy drug. Likewise, Health Canada indicated that an equivalence trial design is preferred<sup>4</sup>. Equivalence is demonstrated when the entire confidence interval (CI) of a given parameter falls within the lower and upper equivalence margins set before the study (Figure 1, from Isakov *et al*, 2016<sup>5</sup>).



**Figure 1** - Testing for equivalence of the potential biosimilar to the originator biologic (Isakov *et al*, 2016).

The sample size was calculated for our primary effectiveness outcome (persistence on treatment). For that, we assumed that the frequency of the outcome at the end of follow-up will

<sup>2</sup> Food and Drug Administration. Guidance for industry. Scientific considerations in demonstrating biosimilarity to a reference product. April 2015. <https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf>

<sup>3</sup> European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues on similar biological medicinal products. December 2014. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2015/01/WC500180219.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf)

<sup>4</sup> Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs. November 2016. [https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt\\_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2016-eng.pdf](https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2016-eng.pdf)

<sup>5</sup> Isakov, L., B. Jin, and I.A. Jacobs, Statistical Primer on Biosimilar Clinical Development. *Am J Ther*, 2016. 23(6): p. e1903-e1910.

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be 70%. We calculated that for each condition (RA, AS, CD, UC) we require a sample size in each treatment group of 100 patients for an approximate total of 800 patients, to demonstrate equivalence between the biosimilar and the legacy drug. This estimate is based on an upper equivalence margin of 1.34 and a symmetrical lower margin of 0.75, with a 5% type I error rate and power of 80%.

### **F. ADVISORY COMMITTEE**

An advisory committee will be established with a dual purpose of providing feedback to CAN-AIM on the current work and developing plans for future biosimilar analyses (these future analyses would be performed under updated protocols with separate funding and timelines). The committee will be mandated to facilitate horizontal management between DSEN partners (CIHR and Health Canada), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Pan-Canadian Pharmaceutical Alliance, and other groups, in terms of project direction and evaluation.

The advisory committee will monitor the project in an ongoing fashion, contributing to the quarterly and final reports on the progress of the project, and work with CAN-AIM on the final set of deliverables. The work of the committee will be conducted for the duration of project, and may be extended as needed. It is anticipated teleconferences will occur on a quarterly basis.

### **G. KNOWLEDGE TRANSLATION (KT) PLAN**

The results of this project will be disseminated in part through traditional methods of dissemination, such as publication in peer reviewed and open access journals and abstracts submitted to national and international meetings. The advisory committee will also advise on the development, implementation and progress of KT activities in this project. We will provide updates to Health Canada via the DSEN coordinating office in two formats: quarterly interim reports and a final report. Through quarterly interim reports we will share information on the status of the project, provide early results from preliminary analysis, as well as inform DSEN about potential modifications of project milestones and/or research protocols as needed. We will also provide a final report, and make use of DSEN contacts with policy makers to ensure that results are adequately disseminated. Dissemination to a wide audience (researchers, policy makers, and other stakeholders) at DSEN-sponsored workshops (such as those held in the context of annual meetings of CADTH and the Canadian Association for Population Therapeutics [CAPT]) may also be possible.

A novel element of our KT plan will be the presentation of our preliminary and final results at stakeholder workshops. This will help us gather information from a wide range of stakeholders (patients, physicians, and policy makers) regarding reasons for our results.

### **H. SUMMARY**

With this proof of concept project, we aim to demonstrate the feasibility of creating a network of clinical cohorts and other resources to provide real-world information on the use of biosimilar drugs in Canada. The core of our proposal revolves around the clinical datasets, but as we will complement that with analyses of national drug patterns using NPDUIS data. CAN-AIM is well-positioned to develop an effective program of research and surveillance related to biologic and biosimilar drugs.

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### **APPENDIX A – Brief description of the clinical cohorts**

#### Canadian Early Arthritis Cohort (CATCH)

CATCH is a successful multicenter ongoing observational cohort study of patients with early RA (ERA) recruiting 300 patients per year and who are followed according to a standardized protocol. The consortium has been actively studying these patients since 2007. CATCH has a network of 19 clinical sites across Canada in both teaching hospitals and community-based hospitals or clinics. CATCH has more than 1,800 patient participants with a regular collection of information about health status, treatments, joint swelling, and overall disease progress.

#### Ontario Best Practices Research Initiative - Rheumatoid Arthritis Registry (OBRI-RA)

OBRI-RA is a clinical registry of RA patients followed in routine care. Data collected includes detailed clinical data, longitudinal evolution of treatments and disease severity, with long-term administrative data on adverse events and health care use.

#### Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in Therapeutics (RAPPORT)

RAPPORT is a prospective cohort registry launched in the Province of Alberta in 2003 and comprises patients with rheumatoid arthritis (RA) psoriatic arthritis. Longitudinal data are collected at baseline, 3 months, and every 6 months thereafter on several clinical and laboratory measures of efficacy (swollen and tender joint count, patient global, patient VAS pain, Health Assessment Questionnaire, Disease Activity Score, C-reactive protein, erythrocyte sedimentation rate, x-rays of hands and feet), safety, employment, health care and community resource utilization, and Health Related Quality of Life. Patients provide outcomes data directly into an online questionnaire.

#### Follow up Research Cohort Ankylosing SpondyliTis (FORCAST)

FORCAST constitutes an integrated health care delivery model whereby patients with ankylosing spondylitis (AS) receive care through a network of health care providers that include rheumatologists and specialist nurse practitioners. Data is collected at baseline, 3 months, and every 6 months thereafter in disease activity and function measures (BASDAI, BASFI, patient global, patient VAS total back pain, nocturnal back pain, SPARCC enthesitis score, BASMI and EDASMI mobility assessment, C-reactive protein, erythrocyte sedimentation rate), drug safety, employment, health care and community resource utilization, and Health Related Quality of Life. Serum and imaging data is collected prospectively.

#### RHUMADATA Clinical Database and Registry

RHUMADATA® has been collecting data for the past 16 years mainly from patients with RA. The database is set up in two centres in Quebec: Centre d'Osteoporose et de Rhumatologie de Quebec (CORQ) in Quebec City, which has an input of 25% of all data, and Institute of Rheumatology Research in Montreal (IRRM), which provides about 75% of all data. Currently, there are approximately 4,000 patients with RA in the database. Data included demographics,

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disease and therapy characteristics. Assessment of disease activity, including BASDAI, BASFI and ASDAS, reasons for discontinuation of a drug, laboratory imaging results.

### Early Undifferentiated PolyArthritis (EUPA) and Biologic Database

This cohort and database collect data on individuals diagnosed with early inflammatory arthritis. The aim is to help define the long-term evolution of inflammatory arthritis by detecting antibodies and other biological markers to determine if they may be useful in predicting the outcome of arthritis. Data is collected at baseline, 6 months, and annually thereafter in disease activity and function measures (X-rays of hands and feet, blood tests including complete blood count, sedimentation rate, protein C-reactive dosage, rheumatoid factor detection), drug safety, employment, health care and community resource utilization, and Health Related Quality of Life. Serum is collected prospectively.

### Canadian IBD Research Consortium (CIRC)

CIRC is a research consortium organized to promote research in inflammatory bowel diseases through collaboration of multiple Canadian centres, including the McGill IBD Centre. CIRC support for Canadian centres like McGill IBD enables further research into the etiology of IBD, effectiveness treatment strategies for IBD and strategies for prevention.

### MUHC Rheumatology and affiliated clinics

Recruitment for RA patients, followed by MUHC rheumatologists, will occur in clinics at MUHC hospitals and affiliated, external clinics in the Montreal area, including the West Island.

### The Arthritis Program Research Group Inc.

The Arthritis Program Research Group Inc. at the Southlake Regional Health Centre in Newmarket, Ontario, is an award winning program committed to delivering the highest standards in arthritis care.

## Study Protocol: Comparative Effectiveness and Safety of Biosimilar and Legacy Drugs

### APPENDIX B – Data collected and study data collection schedule for clinical cohorts.

Domain	Variable	Source	Assessments									
			Baseline	Follow-up								
			0 months	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	54 months
<b>Demographics</b>	Patient's ID	Questionnaire	X	X	X	X	X	X	X	X	X	X
	DOB	Questionnaire	X									
	Sex	Questionnaire	X									
	Education	Questionnaire	X				X		X		X	
	Race/Ethnicity	Questionnaire	X									
<b>BMI</b>	Body Mass Index	Questionnaire	X									
	Weight						X		X		X	
<b>Smoking</b>	Smoking	Questionnaire	X				X		X		X	
	Cigarette quantity	Questionnaire	X				X		X		X	
	Years of smoking	Questionnaire	X				X		X		X	
<b>Major Comorbidities</b>	Congestive heart failure	Questionnaire Administrative database	X				X		X		X	
	Diabetes	Questionnaire Administrative database	X				X		X		X	
	Hypertension	Questionnaire Administrative database	X				X		X		X	
	Coronary artery disease	Questionnaire Administrative database	X				X		X		X	
	Malignancy	Questionnaire Administrative database	X				X		X		X	
	Renal failure	Questionnaire Administrative database	X				X		X		X	
	Other	Questionnaire	X				X		X		X	

## Study Protocol: Comparative Effectiveness and Safety of Biosimilar and Legacy Drugs

		Administrative database										
<b>Hospitalization Data</b>	Hospitalization	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
	Infection hospitalization	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
	Diagnosis	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
	Date	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
	Length of stay	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
<b>Medical services</b>	Physician visits	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
	Specialty	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
<b>Relevant Surgical History</b>	Surgery date	Questionnaire Administrative database	X									
	Surgery description	Questionnaire Administrative database	X									
<b>Infection</b>	Infection event	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
	Infection date	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
	Infection description	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
<b>Diagnosis and</b>	Date of diagnosis	Questionnaire	X									

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<b>disease status</b>	Disease duration	Questionnaire	X									
	Disease status	Questionnaire	X	X	X	X	X	X	X	X	X	X
<b>Clinical evaluation of disease activity and response</b>	DAS-28	Questionnaire	X	X	X	X	X	X	X	X	X	X
	SDAI	Questionnaire	X	X	X	X	X	X	X	X	X	X
	ASAS	Questionnaire	X	X	X	X	X	X	X	X	X	X
	ASDAS	Questionnaire	X	X	X	X	X	X	X	X	X	X
	BASDAI	Questionnaire	X	X	X	X	X	X	X	X	X	X
	BASFI	Questionnaire	X	X	X	X	X	X	X	X	X	X
	mSASSS	Questionnaire	X									
	Joint Count	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Mayo Score or PMS	Questionnaire	X	X	X	X	X	X	X	X	X	X
	CDAI	Questionnaire	X				X					
	HBI	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Disease phenotype	Questionnaire	X									
	Physician's global assessment	Questionnaire	X	X	X	X	X	X	X	X	X	X
<b>Patient reported outcomes QoL</b>	HAQ-DI	Questionnaire	X	X	X	X	X	X	X	X	X	X
	SIBDQ	Questionnaire	X	X	X	X	X	X	X	X	X	X
	EQ-5D	Questionnaire	X				X		X		X	
	VR-12	Questionnaire	X	X	X	X	X	X	X	X	X	X
	VAS (Patient's global assessment)	Questionnaire	X	X	X	X	X	X	X	X	X	X
<b>Imaging</b>	Endoscopy report	Questionnaire	X				X				X	
<b>X-Rays</b>	X ray report	Questionnaire	X				X				X	
<b>Laboratory</b>	WBC	Questionnaire	X	X	X	X	X	X	X	X	X	X



## Study Protocol: Comparative Effectiveness and Safety of Biosimilar and Legacy Drugs

<b>parameters</b>	RBC	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Hg	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Hematocrit	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Platelets	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Creatinine	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Urinalysis	Questionnaire	X	X	X	X	X	X	X	X	X	X
	ESR	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Fecal calprotectin (as available)	Questionnaire	X	X	X	X	X	X	X	X	X	X
	CRP	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Data on therapy drug monitoring	Questionnaire	X	X	X	X	X	X	X	X	X	X
<b>Current Medication</b>	Medication type	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Medication name	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Drug Identification Number (DIN)	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Start date	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Dose	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Frequency	Questionnaire	X	X	X	X	X	X	X	X	X	X
<b>Changes in current medications</b>	Medication type	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Medication name	Questionnaire	X	X	X	X	X	X	X	X	X	X
	DIN	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Stop date	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Reason for stopping medication	Questionnaire	X	X	X	X	X	X	X	X	X	X
<b>Concomitant</b>	Medication type	Questionnaire	X	X	X	X	X	X	X	X	X	X

## Study Protocol: Comparative Effectiveness and Safety of Biosimilar and Legacy Drugs

<b>medications</b>		Administrative database										
	Medication name	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
	DIN	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
	Start date	Questionnaire Administrative database	X	X	X	X	X	X	X	X	X	X
<b>Adverse events</b>	Occurrence adverse events	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Date AE	Questionnaire	X	X	X	X	X	X	X	X	X	X
	Type	Questionnaire	X	X	X	X	X	X	X	X	X	X

## Study Protocol: Comparative Effectiveness and Safety of Biosimilar and Legacy Drugs

### APPENDIX C – Timeline

<i>Year 1 (2018)</i>												
<i>Activity</i>	<i>Month</i>											
	<i>Jan</i>	<i>Feb</i>	<i>Mar</i>	<i>Apr</i>	<i>May</i>	<i>Jun</i>	<i>Jul</i>	<i>Aug</i>	<i>Sep</i>	<i>Oct</i>	<i>Nov</i>	<i>Dec</i>
Analyze early biosimilar use pattern in Canada with NPDUIS data		X	X									
Modification of case report forms if required			X	X	X	X						
Mid-year report								X	X			
Recruitment of participants begins										X	X	X
Review common data dictionary for distributed analyses										X	X	X
Development of detailed statistical analysis plans										X	X	X
<i>Year 2 (2019)</i>												
	<i>Jan</i>	<i>Feb</i>	<i>Mar</i>	<i>Apr</i>	<i>May</i>	<i>Jun</i>	<i>Jul</i>	<i>Aug</i>	<i>Sep</i>	<i>Oct</i>	<i>Nov</i>	<i>Dec</i>
Annual report	X	X										
Recruitment	X	X	X	X	X	X	X	X	X	X	X	X
Mid-year report						X	X					
Pilot query on drug utilization with administrative databases						X	X	X				
Pilot query on discontinuation analysis									X	X	X	
Pilot query on treatment failure										X	X	X
<i>Year 3 (2020)</i>												
	<i>Jan</i>	<i>Feb</i>	<i>Mar</i>	<i>Apr</i>	<i>May</i>	<i>Jun</i>	<i>Jul</i>	<i>Aug</i>	<i>Sep</i>	<i>Oct</i>	<i>Nov</i>	<i>Dec</i>
Annual report	X	X										
Recruitment	X	X	X	X	X	X	X	X	X	X	X	X
Pilot query on clinical outcomes and patient-reported outcomes	X	X	X	X	X	X	X	X	X	X	X	X
Stakeholder workshop					X							
Mid-year report						X	X					
Interim analysis with clinical cohort data						X	X	X	X	X	X	X
<i>Year 4 (2021)</i>												
	<i>Jan</i>	<i>Feb</i>	<i>Mar</i>	<i>Apr</i>	<i>May</i>	<i>Jun</i>	<i>Jul</i>	<i>Aug</i>	<i>Sep</i>	<i>Oct</i>	<i>Nov</i>	<i>Dec</i>
Annual report	X	X										
Recruitment	X	X	X									
Interim analysis with clinical cohort data	X	X	X	X	X							
Mid-year report						X	X					
Additional analysis with clinical cohort data						X	X	X	X	X	X	X
<i>Year 5 (2022)</i>												
	<i>Jan</i>	<i>Feb</i>	<i>Mar</i>	<i>Apr</i>	<i>May</i>	<i>Jun</i>	<i>Jul</i>	<i>Aug</i>	<i>Sep</i>	<i>Oct</i>	<i>Nov</i>	<i>Dec</i>
Annual report	X	X										
Additional analysis with clinical cohort data	X	X	X	X	X	X	X	X	X	X	X	X
Mid-year report						X	X					

# Study Protocol: Comparative Effectiveness and Safety of Biosimilar and Legacy Drugs

Stakeholder workshop									x			
Final report										X	X	X