Annual Progress Report

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Project Title: Improving the Efficiency of Regulatory Decisions for Biosimilars and Interchangeable Biosimilars by Leveraging Real-World Data to Produce Real-World Evidence

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Project Overview

The digital sharing and storage of medical claims and electronic health records have produced volumes of real-world data (RWD) that could advance the production of real-world evidence (RWE) to demonstrate that there is no clinically meaningful difference in the safety and efficacy of biosimilar products. There is a particular opportunity for RWD/RWE to supplement or supplant evidence needs around product switching to meet the biosimilar interchangeability safety standards. While clinical trials are considered the gold-standard for assessing the safety and efficacy of novel biologics, RWD/RWE offers a unique potential in biosimilar and interchangeable biologic development by leveraging prior experience with the reference product or existing biosimilars for comparison and ensuring study populations that are reflective of the patients who receive the products in usual care. RWD/RWE could be used to predict real-world outcomes more accurately. The use of RWD/RWE to improve the efficiency of clinical studies for biosimilar products will speed the development of new biosimilars and speed the process of granting the regulatory designation of interchangeability without requiring a large switching study, thereby minimizing some barriers to biosimilar uptake.

Increasing the efficiency and reducing the cost of biosimilar development by using RWD/RWE could lead to a shorter time to FDA approval. While licensure does not necessarily mean that the biosimilar will reach the market immediately, earlier approval could lead to earlier market access by accelerating the development and marketing timeline. Reducing the cost and time necessary for clinical studies, such as using RWD/RWE for a switching assessment for interchangeability or to optimize patient recruitment and decrease the size of clinical studies to assess treatment effect, provides an incentive for manufacturers to pursue biosimilar development by reducing the financial barrier to market entry. Thirdly, patients and providers have long been interested in RWD/RWE to become more comfortable with using biosimilars in “patients like me,” so including RWD/RWE in the development process could encourage patients and prescribers to adopt biosimilars sooner and more broadly.

Our long-term goal is to evaluate the use of RWD/RWE in biosimilar development by providing biosimilar manufacturers, as well as the broader research community, with tools they can reuse for their own tests of interchangeability and other regulatory questions. The purpose of this study is to assess RWD/RWE and determine its potential to streamline the pre-market regulatory approval process for biosimilars by identifying alternatives to clinical studies to meet regulatory standards. This study will examine whether the current secondary data (e.g., insurance claims or electronic health records) and observational study methods improve the efficiency of clinical studies for biosimilar products or whether more work must be done to improve the quality and rigor of available data and study approaches before it can be applied in the biosimilar regulatory process. Specifically, if incomplete RWD leads to inadequate population size available for research and/or introduces selection or reporting bias, more robust data collection methods may be necessary. If available data sources do not routinely contain variables of interest to biosimilar development, secondary data without linkage to data where those measures are recorded may limit meaningful safety and efficacy assessments. Also, if current observational methodological approaches are not suited to answer questions with regulatory rigor, more robust methods or algorithms may be required.

Our specific goals for this study and current progress for each are described below.

Aim 1: Determine the quality of RWD and the relevance of RWE for biosimilar regulatory decision-making. We will conduct a literature review and convene an expert panel to establish the data needs for regulatory approvals of new biosimilars and designations of

interchangeability. Then we will investigate whether and where RWD/RWE could reasonably be used to address regulatory data needs. We will measure the availability and completeness of RWD in administrative claims and the availability of clinically relevant endpoints or the ability to impute or estimate meaningful outcomes with existing or novel algorithms.

Aim 2: Use RWD/RWE to emulate an FDA evaluation of the interchangeability of a biosimilar drug. We will conduct a target trial emulation of a switching study using RWD/RWE from multiple de-identified datasets representing over 150 million patient lives to define where existing claims data are suited to support biosimilar regulatory assessment and evaluate where data enhancements could improve the fitness of claims data for regulatory use.

Summary of Progress

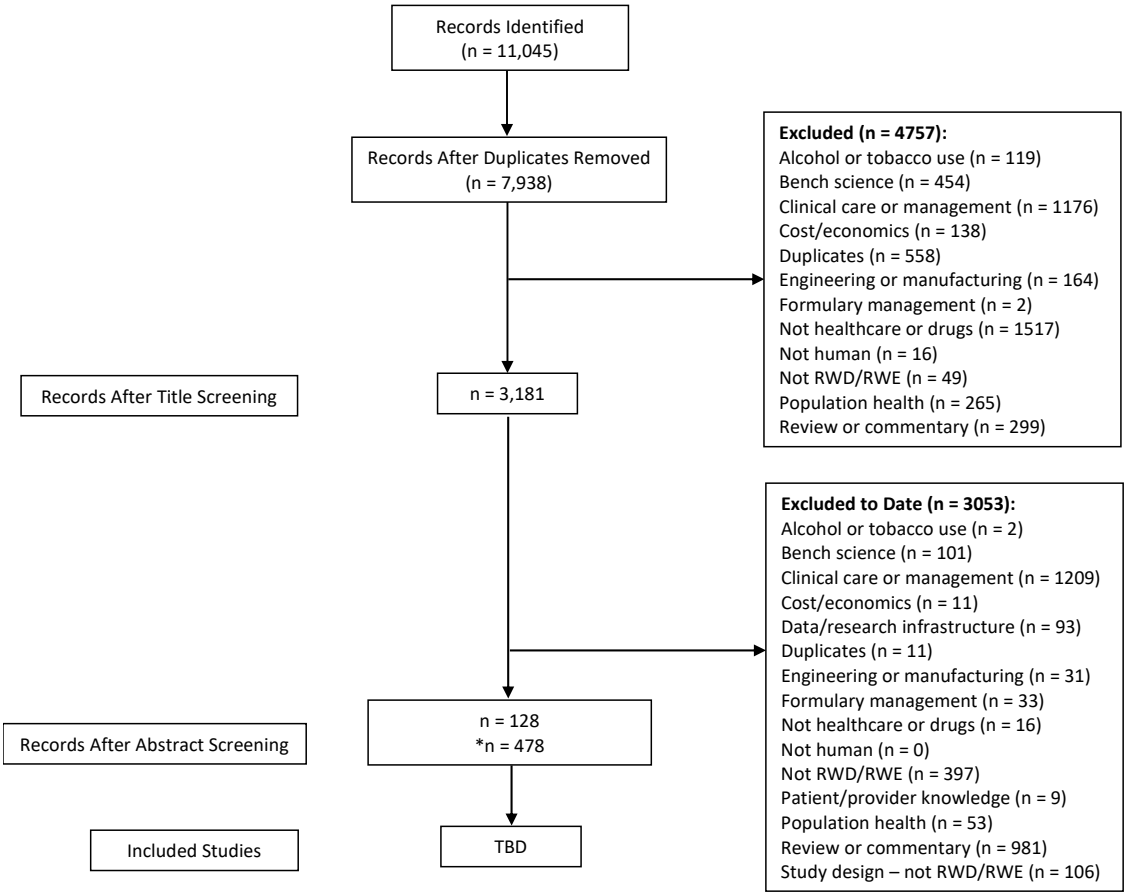
Since beginning this project in September 2022, our focus has been on Aim 1 activities, including a comprehensive literature review and detailed regulatory assessment to identify where RWD/RWE has been or could be used in a regulatory submission for biosimilarity or interchangeability. We have made progress as described below.

Aim 1: Determine the quality of RWD and the relevance of RWE for biosimilars regulatory decision-making.

Aim 1, Task 1: Literature review and regulatory assessment.

A structured, comprehensive literature review is underway to identify studies describing the use of RWD/RWE for regulatory submissions from a global perspective or methods or study designs that could be applied in a regulatory context for biosimilars or interchangeable biologics. **Figure 1** shows the results to date of literature screening.

Two reviewers are independently assessing articles for inclusion and are currently progressing through a full-text review of studies that were retained through title and abstract screening. This includes n = 478 articles that were initially marked for exclusion, but we determined we needed a closer look at the text to identify relevant methods that could be applied to RWD/RWE in a regulatory context or to extract additional articles from the reference lists of select articles. The reviewers are preparing an instrument to extract relevant data from included articles.



*Articles that were provisionally excluded but require a closer look to review methods and references.

Figure 1. PRISMA diagram describing literature review article inclusion and exclusion.

A detailed review of regulatory requirements for biosimilars and interchangeable biologics was also completed to recommend where RWD/RWE has been, or could feasibly be, used for regulatory approval. We found that RWD/RWE has not been used in biosimilar applications; however, we are developing recommendations based on several examples where it was included for small-molecule drugs and in products for oncology or rare diseases, usually as an external control for a single-arm trial.[1-7] Despite the lack of application specifically for a biosimilar or interchangeable biologic development, we identified several areas where a RWD/RWE framework could feasibly be included in the 351(k) biosimilar regulatory assessment:

- Generating hypotheses and study endpoints
- Identifying biomarkers
- Leveraging clinical pathway analysis
- Targeting patients for study recruitment
- Assessing trial feasibility
- Informing statistical model development
- Leveraging disease natural history
- Testing interchangeability
- Creating an external control arm for single-arm trials
- Supporting pragmatic trials in study design or data analysis

The results of both the literature review and regulatory assessment will be prepared as manuscripts for peer-reviewed publication, and full reports expanding on the above findings will be publicly available at www.bbcic.org once finalized and free from any publication embargoes. The results of these detailed analyses will be used to directly inform recommendations that are one key deliverable of this project. These results will also inform our approach to conducting the target trial emulation described in Aim 2.

Aim 1, Task 2: Expert panel to develop actionable recommendations.

For the expert panel, we recruited individuals with expertise in biosimilar development, regulatory requirements, and observational research using secondary data sources. The panel is composed of nine experts with the following skills: biosimilar regulatory and policy expertise (2), observational research methods and study design employed as a consultant or in academia (2), biosimilar development and marketing (3), data analysis using large insurance claims databases (1), and FDA regulatory evaluation (1).

The purpose of the expert panel is to identify not only where RWD/RWE could be used for biosimilar development but also how it could be applied to meet detailed regulatory requirements. Panelists will be asked to complete an anonymous pre-panel questionnaire to set the stage and gather baseline information and initial input that will feed into a Delphi process during the panel meeting. Participants will be asked to identify where they think RWD/RWE could be used with confidence, with caveats, or is unlikely to meet regulatory needs and to identify barriers that must be addressed to realize the potential of RWD/RWE.

During the two-hour virtual meeting, panelists will be asked to reflect on the results of the pre-panel questionnaire and the regulatory assessment provided before the meeting. Three hypothetical case studies will be introduced and provide realistic scenarios in biosimilar or interchangeable biologic development to illicit detailed discussion and recommendations specifically where and how RWD/RWE could or should be incorporated into materials for regulatory assessment. One case study describes the first biosimilar in development for the treatment of a rare cancer to elicit ideas for how to use RWD/RWE to optimize a clinical study. The panel will also consider recommendation changes if the biosimilar was intended for a more common disease. The second case study describes a biosimilar in development for a relatively common disease where biosimilars are already available for the reference product, but only outside the United States. Panelists will assess the challenges and opportunities of using international data from an operational and United States regulatory perspective. The panel will also consider study designs and what additional considerations are needed if the sponsor sought an interchangeability designation simultaneously. The final case study hinges on using RWD/RWE for an interchangeability designation for a biosimilar treating a relatively common disease for which there are existing biosimilars to the same reference product available in the United States. The hypothetical case studies and related discussion questions prepared for the panel are included in **Appendix 1**.

From these panel activities, we will prepare a detailed report including recommendations and strategies for incorporating RWD/RWE in biosimilar and interchangeable biologic development from a regulatory perspective in the United States. Results will be disseminated as an abstract to be presented at a relevant scientific or professional meeting, and a manuscript will be prepared for peer-reviewed publication.

Aim 1, Tasks 3 and 4: Quality of RWD and Relevance of RWE.

Tasks 3 and 4 in Aim 1 will result in an assessment of the completeness and availability of relevant data elements in administrative claims, evaluating the fitness of using these data to emulate a clinical study described in Aim 2. A preliminary summary of eight existing clinical studies (four completed, four ongoing at the time of this report) evaluating the outcomes of a reference product and biosimilar switching to assess interchangeability (see Aim 2, Task 1). We tabulated a description of each study design and a list of covariates and endpoint measures as the starting point for evaluating the fitness of our available data from one large national health insurer and one regional integrated delivery network. We will first identify which variables are available in our databases, followed by assessing the completeness and relevance for emulating an interchangeability clinical study. Specifically, we will test our ability to measure covariates and study outcomes directly. If endpoints are not available in claims (e.g., pharmacokinetic parameters or patient reported outcomes), we will identify or develop algorithms to serve as surrogate measures of safety and efficacy when direct observations are not available.

Aim 2: Use RWD/RWE to emulate an FDA evaluation of interchangeability of a biosimilar drug.

Aim 2, Task 1: Test case selection.

We conducted a literature scan of peer-reviewed databases (e.g., MEDLINE) and records at clinicaltrials.gov to identify existing studies that have been used or are in progress to assess interchangeability for regulatory evaluation. The products with existing trials include insulin glargine, adalimumab, ranibizumab, infliximab, ustekinumab, rituximab, and bevacizumab. Each study was abstracted and tabulated according to drug product, comparator, patient inclusion, and exclusion criteria, patient baseline characteristics, study design, and endpoints measured. From the study details and data assessment conducted in Aim 1, Tasks 3 and 4, we will select one study we believe will most likely lead to a successful emulation using RWD in the BBCIC network based on the outcomes of Aim 1, Tasks 3 and 4 above.

Aim 2, Task 2: Target trial emulation.

The BBCIC Research Team has begun planning clinical study emulation of the test case selected in Aim 2, Task 1 using only RWD from two Research Partners in the BBCIC network – one large national insurer and one regional integrated delivery network. A protocol will detail our RWD study design according to the test case and following best practices for target trial emulation. Hernan and Robins [REF] established seven elements for an emulation: patient eligibility criteria, treatment strategies being compared, assignment procedures, follow-up period, the outcome of interest, causal contrast(s) of interest, and analysis plan. This will outline our emulation approach and guide our study design.

Aim 2, Task 3: Data analysis.

The emulation protocol will include a comparison of study designs to evaluate the fitness of existing RWD from administrative claims to replicate the selected clinical study. Results from the emulation, including patient characteristics, outcomes, and any applied algorithms, will be compared in detail with the test case. We will also conduct a detailed assessment of how our RWD performed according to each element in the emulation scheme.

Regulatory Impact

RWD/RWE has the potential to improve the efficiency of regulatory decision-making for biosimilars. This study will determine whether the currently available RWDRWD from administrative claims and current observational research methods are ready to use in biosimilar product development or whether more work must be done to improve the quality and rigor of the data or study approach. The results of this study will be impactful to the FDA as they consider additional guidance documents for the use of RWD/RWE for biosimilar development.

Our work will aid biosimilar manufacturers, regulatory decision-makers, and the research community as a whole to leverage RWD/RWE for biosimilar development and licensure, specifically in the test of interchangeability. This study will advance the development of interchangeable products by providing new information on the quality of the data in multiple claims databases and developing new analytical tools for the evaluation of interchangeability. These analytical tools will provide generalizable strategies to leverage relevant RWE in regulatory science. New analytical tools and a proposed framework for incorporating RWD/RWE into product development will include data harmonization, patient matching, and data provenance for the elements we will identify and use in this study to complement existing data models and analytical tools. These will be valuable assets that could be used by drug sponsors for future regulatory approvals and designations as interchangeable biosimilars.

Communication and Dissemination

As we are still conducting tasks associated with Aim 1, there have not been any public communications to date; however, two abstracts are in preparation for submission to ISPOR Europe, a scientific meeting focused on pharmacoepidemiology, with a submission deadline in June and a presentation in late 2023. One abstract will include the results of the literature review, and one will describe the results of the regulatory assessment of RWD/RWE as discussed in Aim 1, Task 1.

Challenges

None to report.

Next Steps

Aim 1 activities are nearing completion and planning for Aim 2 is underway. Specifically, abstracts are in preparation for the literature review and regulatory assessment described in Aim 1, Task 1. A manuscript is planned to describe the literature review and another to describe the regulatory assessment and recommendations that emerge from the expert panel described in Aim 2, Task 2. The Research Team is working to finalize the measures and parameters for data quality and relevance assessments (Aim 2, Tasks 3, and 4) and expect to conduct the evaluation by the end of Year 1 activities, followed by at least one abstract to report the findings. The Research Team is also beginning the process of test case selection for emulation as described in Aim 2, Task 1. Protocol planning is underway and will commence in earnest upon the final selection of the target trial. Once the protocol is finalized, the programmers and analysts will prepare data queries and analytic programs to develop the emulation data set, followed by data analysis. Abstracts designated for scientific or professional meetings and a final manuscript describing the target trial emulation will be prepared for peer-reviewed publication.

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Appendix 1. Expert Panel Case Studies

Case Study 1. Biosimilar approval, rare cancer

Product X is being developed as a biosimilar for the reference biologic Product A which is used for the treatment of a rare cancer. Biologic Product A has been marketed for 20 years and has an established safety profile. Product X would be the first biosimilar approved in reference to biologic Product A, both in the US and internationally. There is still some residual uncertainty around Product X's biosimilarity after comparative analytical assessments; several clinical studies will be necessary to fully address this uncertainty. Clinical studies are well underway, but recruitment is costly and challenging. The sponsor plans to use RWD from a linked EHR-registry database to better understand utilization among patients treated with Product A, and to potentially target eligible patients who are currently under-represented in the ongoing clinical trials.

Pre-panel question:

a. How would you change or improve upon this strategy using RWD?

Questions for discussion on July 10

b. Questions about RWD sourcing:
    i How feasible is it currently to use an HER-registry database to target patients with rare conditions for recruitment?
    ii With the availability of linked data still somewhat limited, what suggestions do you have for where to focus data infrastructure improvements?
    iii What other RWD sources would you explore for improving recruitment? Why would the other data sources be useful in this case?
c. Questions about RWD use:
    i What innovative ways could RWD be used to improve clinical trial enrollment overall and target patients for comparative immunogenicity studies?
    ii How could RWD be used to reduce the size of an RCT, or potentially justify whether small, descriptive safety studies could be used rather than those powered on safety/efficacy endpoints?
    iii Outside of single-arm studies, what innovative study designs that leverage RWD could be used to both speed up development and support regulatory approval?
d. Overall assessment:
    i In this context, does RWD seem like a useful tool for creating efficiencies in Product X's clinical development?
    ii If not, what additional contextual conditions surrounding Product X and/or what additional RWD/methods would be necessary?
    iii What considerations would change if this was for a more common disease?

Case Study 2. Biosimilar approval, common inflammatory condition

Product Y is being developed as a biosimilar for the treatment of a common inflammatory condition. There are several biosimilars approved for reference biologic Product B, but only in international settings. There is little residual uncertainty around the products biosimilarity after comparative analytical assessments. The sponsor plans to conduct an additional comparative PK/PD clinical study. In lieu of any additional comparative clinical studies, the sponsor plans to use RWD from Country X's national health system to evaluate safety and effectiveness using a target trial emulation study design. Country X's EHRs have rich clinical data and patient history.

Pre-panel question:

e. How would you change or improve upon this strategy using RWD?

Questions for discussion on July 10

f. Questions about RWD sourcing:
    i What internationally-sourced RWD could be used for comparative clinical assessments? Provide examples.
    ii What are important considerations for using international data for US regulatory purposes?
g. Questions about RWD use:
    i What are some alternatives to the traditional comparative immunogenicity assessments that use RWD?
    ii What real-world study designs, methods, and/or data could be used in place of the traditional comparative immunogenicity assessments or other clinical studies?
    iii How would these be able to meet regulatory requirements? If they don't, how would they help to speed up clinical development and approval?
    iv What are their strengths/limitations from both an operational and regulatory perspective?
h. Overall assessment:
    i In this context, does RWD seem like a useful tool for creating efficiencies in Product Y's clinical development?
    ii If not, what additional contextual conditions surrounding Product Y and/or what additional RWD/methods would be necessary?
    iii What considerations would change if this was a less common disease?

Case Study 3. Biosimilar interchangeability determination, common inflammatory condition

Biosimilar Product Z is under development as an interchangeable biosimilar for reference biologic Product C which treats a common inflammatory condition; it has been approved and marketed as a biosimilar for five years. There are several other biosimilars approved for reference biologic Product C in the US, but this will be the first interchangeable. The sponsor conducted a thorough clinical pathway analysis in one health system's EHR to better understand how Product Z and all other approved biosimilars for Product C are used in real-world clinical practice. The sponsor determined they would not conduct an immunogenicity assessment within a traditional switching study and instead conduct noninferiority studies using RWD from a large claims database.

Pre-panel question:

i. How would you change or improve upon this strategy using RWD?

Questions for discussion on July 10

j. Questions about RWD sourcing:
    i What RWD claims databases could be used for noninferiority studies?
    ii What suggestions do you have for where to focus data infrastructure improvements to make such studies more feasible?
k. Questions about RWD use:
    i Would a more traditional switching study (including a comparative immunogenicity assessment) be necessary in this context – why or why not?
    ii Where does RWD fit on the decision tree for the need for a traditional switching study?
    iii When is a switching study needed? When is a switching study not needed?
    iv How would this change if the biosimilar was not already marketed? For example, if the sponsor is submitting for simultaneous interchangeability or the sponsor is submitting for an interchangeability approval without real-world exposure data.
    v How else could RWD be used to support an interchangeability designation?
l. Overall assessment:
    i In this context, does RWD seem like a useful tool for creating efficiencies in Product Z's clinical development?
    ii If not, what additional contextual conditions surrounding Product Z and/or what additional RWD/methods would be necessary?