# Can observational studies replace switching studies for evaluating the interchangeability of biological drug originators and biosimilars? Methodological challenges and considerations

**Chiara Bellitto**[1], Andrea Spini[1], Catherine M. Lockhart[2], Giorgia Pellegrini[1], Luca L'Abbate[1], Ylenia Ingrasciotta[1], Marco Massari[3], Flavia Mayer[3], Mette Reilev[4], Julie Rudbech Krumborg[4], Jesper Hallas[4], Gianluca Trifirò[1]

[1]Department of Diagnostics and Public Health, University of Verona, Verona, Italy
[2] Biologics and Biosimilars Collective Intelligence Consortium, Alexandria, VA, USA
[3] Italian National Institute of Health, Rome, Italy
[4] Clinical Pharmacology, Pharmacy, and Environmental Medicine, University of Southern Denmark, Denmark

## Background

- **Biological drugs** have significantly improved the management of several **chronic diseases**, offering targeted therapeutic options and better quality of life for many patients[1]. However, their high costs and increasing use have contributed to escalating healthcare costs globally, which might lead to significant equity problems, unmet needs, and strain on healthcare expenditure[2,3].

- After the expiration of market exclusivity and patent protection period for innovative biological drugs (i.e., **reference products**), competing manufacturers are allowed to sell similar versions of these medications (i.e., **biosimilars**).

- The term "**biosimilars**" was first introduced in 2006 in the European Union (EU) to describe biological medicines developed as copies of reference products[4].

- **Regulatory frameworks differ across regions**: all biosimilars approved in the EU are considered interchangeable with their reference products. In the US, interchangeability is a distinct regulatory status under the Biologics Price Competition and Innovation Act (BPCIA) of 2009, initially requiring switching studies[5,6]. In switching studies, patients already in stable treatment with a reference product are treated with alternating regimens of reference and biosimilars and compared to those who did not receive alternating treatment regimens[7].

- Switching studies can be time-consuming and expensive, and, so far, only a limited number of biosimilars have achieved interchangeability in the US. Thus, **following updated FDA guidance in June 2024, such studies are no longer required**[8].

- **Real-World Data (RWD) and Real-World Evidence (RWE)** is increasingly recognized as a valid tool to support regulatory decision-making, including monitoring switching patterns and benefit-risk profiles of biosimilars[9].

## Aim

The aim is to share the **methodological challenges and considerations** in conducting observational studies, such as target trial emulation (TTE), to evaluate **switching from reference biologics to biosimilars** in different countries.

## 1 Feasibility assessment

To determine whether observational data collected from non-US healthcare databases can be considered fit-for-purpose to inform regulatory decision-making in the US.

## 2 Target Trial Emulation Protocol

A protocol for the TTE will be developed following the TARGET guidelines (Target Trial Emulation for Real-World Evidence Studies).

The design of the target trial will be tailored to the trials identified in the scoping review, while eligibility criteria and outcomes will be defined based on the data available from the feasibility assessment.

Identify **measured data elements** (e.g., exposures, demographic and clinical elements, outcomes) from **clinical trials that supported regulatory approval of biosimilars** by the FDA and the EMA through a scoping review.

- Comparison of the **regulatory framework** across countries.
- Detailed description of **data sources**.
- Descriptive analyses on **incident users of reference product or biosimilar** across countries.
- Evaluation of **data quality**, including application of eligibility criteria, assessment of outcomes **availability and completeness**, and distribution of standardized mean differences for each covariate across data sources.

### Eligibility criteria

Select meaningful inclusion and exclusion criteria for the target trial.

**Lead-in phase**: only subjects who stay in stable treatment with a reference product for a prespecified time period (e.g., six months) should be included.

**Heterogeneity in data sources and healthcare systems across countries:** the same eligibility criteria may not be equally effective in identifying clinical events and covariates.

### Treatment assignment and Follow-up

Appropriately assigning **initiation of follow-up among non-switchers** to avoid immortal time bias. At $T_0$ different approaches can be applied:

1) the "**clone-censor-weight approach**", in which each eligible subject will be cloned and assigned at each arm;

2) the "**new-switcher design**" in which each switcher should be randomly matched to a prespecified number of individuals who continue treatment with the reference product up to the time point corresponding to the switching date among switchers.

### Causal contrasts

When evaluating the switch, consider «**as-treated**» approach.

### Statistical analysis

- Adjustment for **calendar time.**
- Cox regression analysis with time varying covariates**.**
- **Sensitivity analyses** to explore the potential impact of the COVID-19 pandemic on healthcare utilization.
- Use of **directed acyclic graphs** (DAGs) to guide confounding adjustment by identifying appropriate covariates based on subject-matter knowledge and causal assumptions.

*Key challenges in in designing TTE-based observational studies on biosimilar switching.*

## Expected outcomes and Future perspectives

- Comparison of patient populations and variables (including measurable outcomes) availability across countries using RWD is a necessary step to assess **data fitness-for-use.**
- Harmonization of study design elements across heterogeneous data sources to enable meaningful **cross-country comparisons.**
- Given the focus on **non-medical switching** among patients in stable treatment with reference product, populations are expected to be **comparable across settings.**
- Findings are expected to show **similar outcomes between patients who switch to biosimilars and those continuing reference** treatments.
- Results may support the use of well-designed observational studies as complementary evidence to switching trials.
- Evaluate the **transportability of outcomes** to enhance generalizability across healthcare systems, thereby informing regulatory decisions and public health strategies.

*This project is fully supported by a cooperative agreement (Award #1U01FD007757) with the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS). The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.*

References

Contact