Economic Impact of Non-Medical Switching from Originator Biologics to Biosimilars: A Systematic Literature Review

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ABSTRACT

Introduction: A systematic literature review was conducted to review and summarize the economic impact of non-medical switching (NMS) from biologic originators to their biosimilars (i.e., switching a patient’s medication for reasons irrelevant to the patient’s health).

Methods: English publications reporting healthcare resource utilization (HRU) or costs associated with biosimilar NMS were searched in PubMed and EMBASE over the past 10 years and from selected scientific conferences over the past 3 years, along with gray literature for all biologics with an approved biosimilar (e.g., tumor-necrosis factor inhibitors, erythropoiesis-stimulating agents, insulin and hormone therapies).

Results: A total of 1311 publications were retrieved, where 54 studies met the selection criteria. Seventeen studies reported increased real-world HRU or costs related to biosimilar NMS, e.g., higher rates of surgery (11%), steroid use (13%) and biosimilar dose escalating (6–35.4%). Among the studies that the estimated cost impact associated with NMS, 33 reported drug costs reduction, 12 reported healthcare costs post-NMS without a detailed breakdown, and 5 reported NMS setup and managing costs. Cost estimation/simulation studies demonstrated the cost reduction associated with NMS. However, variation across studies was substantial because of heterogeneity in study designs and assumptions (e.g., disease areas, scenarios of drug price discount rates, cost components, population size, study period, etc.).

Conclusion: Real-world studies reporting the economic impact of biosimilar NMS separately from drug costs are emerging, and those that reported such results found increased HRU in patients with biosimilar NMS. Studies of cost estimation have been largely limited to drug prices. Comprehensive evaluation of the economic impact of NMS should incorporate all important elements of healthcare service needs such as drug price, biologic rebates, HRU, NMS program setup, administration and monitoring costs.
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**Keywords**: Biologics; Biosimilar; Drug costs; Non-medical switching; Pharmacology; Systematic literature review

## INTRODUCTION

Biologics are large complex molecules, or mixtures of molecules, that have revolutionized the treatment of many chronic diseases, including diabetes, hemophilia, hepatitis, cystic fibrosis, growth deficiency, several types of cancer and autoimmune diseases such as rheumatoid and psoriatic arthritis, psoriasis and inflammatory bowel disease [1, 2]. In recent years, a number of biologics have reached the end of their market exclusivity; many biosimilars, biopharmaceutical drugs designed to have active properties similar to their reference biologics, have been developed or are under development [3]. Unlike generic versions of synthetic small-molecule drugs, biosimilars are not exact copies but only highly similar to the approved reference biologics (i.e., originator biologics) [3, 4]. This is due to the intrinsic manufacturing variability of biologics, which inevitably, for large biologic molecules, leads to a degree of structural differences between originator and biosimilar products [3, 4]. However, within an acceptable range of variations that have been clearly defined by regulatory agencies in the USA, Europe and other countries, a biosimilar is required to be highly similar to an originator biologic without functional consequences in terms of efficacy, safety, potency, pharmacokinetic parameters and immunogenicity [3, 4].

Biosimilars may be priced lower than the originator biologics because the research and development processes are typically shorter and less labor-intensive with more relaxed regulatory requirements [4]. In Europe, since the first biosimilar was approved in 2006 there have been over 40 biosimilars on the market [5]; depending on the type, biosimilars have been priced 25–70% less than their originators [4, 6]. In the US, discounts for biosimilars are generally smaller than the discounts for biosimilars in Europe [4, 7]. For instance, the first two biosimilars approved by the US Food and Drug Administration (FDA), filgrastim and infliximab, had a list price of only 15% lower than their originator biologics [3, 7]. Since then, other biosimilars have been launched to the US market at similar discounted rates, with the highest discount to date being 35% for an infliximab biosimilar [7, 8].

Non-medical switch (NMS) refers to switching a patient’s medication for reasons other than a patient’s health and safety. In the past, NMS of small-molecule drugs from branded to their generic versions resulted in significant cost savings for both patients and payers due to the lower drug prices of generic medications [9–11]. However, the economic impact of an originator-to-biosimilar NMS is more complex given that the two drugs are not always identical, and a comparison based only on drug costs would not provide a full picture of the economic implications of NMS [4, 11, 12]. For instance, studies have identified costs associated with biosimilar NMS including costs of training physicians and nurses, pre-NMS planning (e.g., laboratory tests), post-NMS monitoring (e.g., laboratory tests or medical visits following dose adjustments or side effects) and NMS-related administrative procedures (e.g., prior authorization or new reimbursement procedures) [12, 13]. Specifically in the US, a combination of rebates and discounts that biologics manufacturers offer to payers and pharmacy benefits managers may result in comparable purchase prices for originators and biosimilars, effectively reducing or even eliminating the cost advantage of biosimilar NMS [4, 7, 12].

In light of the increasing number of biosimilars on the market and in development worldwide, consideration of the cost implication of biosimilar NMS is important [14]. We conducted a systematic review of the literature to assess and summarize the healthcare resource utilization (HRU) and costs reported for patients undergoing biosimilar NMS.

## METHODS

### Literature Search

A systematic literature review was conducted in September 2018 to identify published studies
reporting data on the HRU and/or costs associated with biologic-to-biosimilar NMS. The literature review was designed, performed and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [15]. Full-text articles published in English between January 2008 and September 2018 were searched using the PubMed and EMBASE databases. In addition, to capture results from recent studies that might not have been published as full-text articles at the time of the search, key conference proceedings of disease areas that may be treated with biologics/biosimilars from 2014 to 2018, depending on availability, were searched using the websites of the following conferences:

- American College of Rheumatology Annual Meeting (ACR/ARHP)
- American College of Gastroenterology Annual Scientific Meeting (ACG)
- American Diabetes Association Scientific Sessions (ADA)
- American Society of Hematology Annual Meeting (ASH)
- American Thoracic Society International Conferences (ATS)
- Annual Meeting of the European Association for the Study of Diabetes (EASD)
- American Society of Clinical Oncology Annual Meeting (ASCO)
- European League Against Rheumatism Annual Congress (EULAR)
- European Congress of Endocrinology (ECE)
- European Society of Cardiology Annual Congress (ESC)
- European Crohn’s and Colitis Organization Annual Congress (ECCO gastro)
- International Society for Pharmacoeconomics and Outcomes Research Annual European Congress (ISPOR Europe)
- International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting (ISPOR International)
- Scientific Sessions of American Heart Association (AHA)
- European Cancer Congress (ECCO cancer).

Search terms included “biosimilar”, “biosimilar agent”, the names of individual biosimilars (e.g., “etanercept”, “epoetin alfa biosimilar”, “filgrastim biosimilar”, etc.), “HRU”, “health resources”, “resource utilization”, “cost”, “health care costs”, “non-medical reasons”, “switch” and other various terms related to HRU, costs and NMS (Electronic Supplementary Table S1). Boolean operators and MeSH terms were used in PubMed and EMBASE databases. For conference proceedings, where search engines were not as rigorous as PubMed and EMBASE and no Boolean operators were available, simple search terms (e.g., biosimilar, non-medical switching, NMS, switching) were used. Finally, a search of the gray literature was conducted using Google Scholar to identify any relevant studies not captured by the database or conference proceeding search.

**Literature Screening**

Inclusion and exclusion criteria were defined a priori (Table 1). Based on these criteria, the articles identified during the PubMed/EMBASE search were screened in two levels: in level one, all articles were screened based on their title and abstract and, in level two, those meeting the inclusion criteria were screened based on their full text using the same criteria as in level one. In level one, when decisions to include or exclude a publication could not be made based solely on its title and abstract, the full text was obtained and screened as part of level two. The title and abstracts of conference proceedings were screened in level one; no level two screening was performed as the full text was not available.

To ensure accuracy, the screening of both publications and conference proceedings was conducted by two reviewers independently. In case of disagreement between the two reviewers, a third reviewer was consulted to reach a consensus.

**Data Extraction and Analysis**

After screening, data extraction was performed by one reviewer and subsequently audited by a second reviewer to ensure accuracy. The data extracted from the identified publications and conference proceeding, whenever available, were the following: publication year, name of
| Disease areas                                      | Citations          | Publication type | Study type          | Biosimilar       | Total population | Time horizon |
|---------------------------------------------------|--------------------|------------------|---------------------|------------------|------------------|--------------|
| Rheumatology, dermatology and gastroenterology   | Jha 2015 [46]      | Abstract         | Simulation study    | Biosimilar infliximab | NR              | 1 year       |
|                                                  | Jha 2015 [47]      | Journal article  | Simulation study    | Biosimilar infliximab | 3,750,611       | 1 year       |
|                                                  | Ala 2016 [48]      | Abstract         | Center-based cohort study | Biosimilar infliximab | 21              | 6 months     |
|                                                  | Becciolini 2016 [49] | Abstract        | Simulation study    | Biosimilar etanercept | NR              | 3 years      |
|                                                  | Bhattacharyya 2016 [50] | Abstract        | Simulation study    | Biosimilar etanercept | 27,052          | 1 year       |
|                                                  | Bocquet 2016 [51]  | Abstract         | Simulation study    | Biosimilar infliximab | 5,483           | 1 year       |
|                                                  | Rahmany 2016 [52]  | Abstract         | Center-based cohort study | Biosimilar infliximab | 88              | 6 months     |
|                                                  | Shah 2016 [53]     | Abstract         | Simulation study    | Biosimilar infliximab | 7,343           | 1 year       |
|                                                  | Sheppard 2016 [34] | Abstract         | Center-based cohort study | Biosimilar infliximab | 25              | 1 year       |
|                                                  | Trancart 2016 [54] | Abstract         | Simulation study    | Biosimilar etanercept | 45,903          | 3 years      |
|                                                  | Alexandre 2017 [55] | Abstract        | Simulation study    | Biosimilar etanercept | 3,142           | 5 years      |
|                                                  | Barnes 2017 [38]   | Abstract         | Simulation study    | Biosimilar etanercept | NR              | NR           |
|                                                  | Dyball 2017 [36]   | Abstract         | Center-based cohort study | Biosimilar etanercept | 38              | NR           |
|                                                  | Glintborg 2017 [16] | Abstract       | Registry/National database | Biosimilar infliximab | 769             | 1 year       |
|                                                  | Gomez 2017 [56]    | Abstract         | Simulation study    | Biosimilar adalimumab | 326             | 1 year       |
| Disease areas | Citations       | Publication type | Study type                   | Biosimilar          | Total population | Time horizon |
|--------------|-----------------|------------------|------------------------------|---------------------|------------------|--------------|
|              | Gutermann 2017  | Abstract         | Center-based cohort study    | Biosimilar infliximab | 333              | 10 months    |
|              | Plevris 2017    | Abstract         | Center-based cohort study    | Biosimilar infliximab | 161              | NR           |
|              | Ratnakumaran 2017 | Journal article | Center-based cohort study    | Biosimilar infliximab | 210              | 1 year       |
|              | Razanskaite 2017 | Journal article | Center-based cohort study    | Biosimilar infliximab | 143              | 1 year       |
|              | Rodriguez 2017  | Abstract         | Center-based cohort study    | Biosimilar infliximab | 72               | 1 year       |
|              | St. Clair Jones 2017 | Abstract     | Center-based cohort study    | Biosimilar infliximab | 71               | 6 months     |
|              | Szlumper 2017   | Abstract         | Center-based cohort study    | Biosimilar etanercept | 39               | 3 months     |
|              | Szlumper 2017   | Abstract         | Center-based cohort study    | Biosimilar etanercept | 109              | 7 months     |
|              | Barnes 2018     | Abstract         | Interview                    | Biosimilar etanercept | 627–689          | NR           |
|              | Garcia-Fernandez 2018 | Abstract   | Center-based cohort study    | Biosimilar infliximab | 76               | 8 months     |
|              | Gibofsky 2018   | Abstract         | Simulation study             | NR                  | 5000             | < 1 year     |
|              | Gibofsky 2018   | Journal article  | Simulation study             | NR                  | 1000             | 3 months     |
|              | Glintborg 2018  | Journal article  | Registry/National database   | Biosimilar infliximab | 769              | 1 year       |
|              | Healy 2018      | Abstract         | Center-based cohort study    | Biosimilar infliximab | 60               | 1 year       |
|              | Husereau 2018   | Journal article  | Simulation study             | Biosimilar infliximab | NR               | NR           |
|              | Ma 2018         | Abstract         | Center-based cohort study    | Biosimilar etanercept | 50               | 6 months     |
|              | Mora 2018       | Abstract         | Center-based cohort study    | Biosimilar infliximab | 18               | 1 year       |
Table 1 continued

| Disease areas | Citations | Publication type | Study type | Biosimilar | Total population | Time horizon |
|---------------|-----------|-----------------|------------|-------------|------------------|--------------|
| Nisar 2018    | Abstract  | Center-based cohort study | Biosimilar rituximab | 39 | 1 year          |
| O’Brien 2018  | Abstract  | Center-based cohort study | Biosimilar infliximab | 20 | 8 months        |
| Peral 2018    | Abstract  | Simulation study | Biosimilar etanercept | NR | 1 year          |
| Rodriguez 2018| Abstract  | Center-based cohort study | Biosimilar infliximab | 48 | 11 months       |
| Shah 2018     | Abstract  | Center-based cohort study | Biosimilar etanercept | 151 | 1 year          |
| Shah 2018     | Abstract  | Center-based cohort study | Biosimilar etanercept | 151 | 6 months        |
| Valido 2018   | Abstract  | Center-based cohort study | Biosimilar infliximab | 60 | 1 year          |
| Zahorian 2018 | Abstract  | Center-based cohort study | Biosimilar infliximab | 110 | NR              |
| NHL, multiple myeloma, colorectal and breast cancer | Abraham 2014 Journal article | Simulation study | Biosimilar epoetin alfa | 100,000 | 15 weeks |
| Sun 2015      | Journal article | Simulation study | Biosimilar filgrastim | 10,000 | 14 days |
| McBride 2017  | Abstract  | Simulation study | Biosimilar filgrastim | 20,000 | Chemotherapy of 1 or 6 cycles |
| McBride 2017  | Abstract  | Simulation study | Biosimilar filgrastim-sndz | 20,000 | 5, 7, 11, 14 days |
| McBride 2017  | Journal article | Simulation study | Biosimilar filgrastim-sndz | 20,000 | 1–14 days |
| Peck 2017     | Abstract  | Center-based cohort study | Biosimilar filgrastim | 100 | 1 year          |
conference (for conference proceedings), country, drug information (originator and biosimilar brand name), study design (study type, data source, number of cohorts or treatment groups, study period and outcomes), study population (disease area, sample size, prior treatment experience with originator, switch rate, biosimilar discontinuation rate and biosimilar-to-biologic switch-back rate), cost and/or HRU input (data source, cost and/or HRU component considered, assumptions, cost year, currency and cost unit) and cost and/or HRU outcomes (HRU and/or cost differences between biosimilars and originators). The extracted data pertaining to study characteristics and design are summarized in Table 1, post-NMS HRU in Table 2 and post-NMS drug costs in Table 3. When extracting drug costs, due to large variations in study design, study population, biosimilar-to-biologic switch-back rate and study duration, total drug costs were calculated per switched population. Annual drug costs and annual total healthcare costs were summarized based on studies directly reporting annual costs. All costs were converted and inflated to 2018 euro (€). Due to the substantial variation in study designs and outcomes, no meta-analysis was conducted. Extracted data were descriptively summarized to retain most of the information identified from the identified studies.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

**RESULTS**

**Study Selection**

A total of 1311 studies were retrieved for screening during the literature search: 383 were
Table 2  Post-NMS HRU and HRU-related costs

| Citations        | Diseases                              | Study type               | Biosimilar     | Time horizon | Data source                        | Reported HRU                                                                                                                                                                                                 |
|------------------|---------------------------------------|--------------------------|----------------|--------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Flodmark 2013    | Pediatric growth disturbances         | Center-based cohort study| Biosimilar     | About 3 years| Hospital data                     | Twelve patients experienced injection-site pain, three required an extra visit to the responsible physician or specialized nurse, 10 required extra phone contact with the physician/nurse                                                                                       |
| Minutolo 2016    | Hemodialysis                          | Center-based cohort study| Biosimilar     | 36 weeks     | 11 nonprofit Italian dialysis centers | Thirty-five percent of patients switched experienced dose escalation                                                                                                                                                                                                  |
| Glintborg 2017   | Rheumatology                          | Registry/National database| Biosimilar     | 1 year       | Danish quality registry, DANBIO   | The mean rate of days with services provided was 5.4 before the switch and 5.7 after switch ($p = 0.0003$)                                                                                                                                                               |
| Peck 2017 [25]   | Multiple myeloma, non-Hodgkin lymphoma| Center-based cohort study| Biosimilar     | 1 year       | Hospital data                     | Use of Plerixafor (bone marrow stimulant) was higher in the biosimilar G-CSF group compared with the originator product (18 vs. 5 patients)                                                                                                                                  |
| Phillips 2017    | All authorized indications            | Registry/National database| Biosimilar     | 1 year       | Turkish healthcare administrative database | Patients who switched to CT-P13 had higher outpatient (€86.6 vs. €58.3; $p = 0.005$), inpatient (€20.6 vs. €9.3; $p = 0.313$) and pharmacy costs (€474.2 vs. €427.9; $p = 0.371$), which resulted in significantly higher total health care costs (€646.8 vs. €528.0; $p = 0.046$) compared to patients who continued infliximab |
| Citations | Diseases                  | Study type                  | Biosimilar       | Time horizon | Data source                      | Reported HRU                                                                 |
|-----------|---------------------------|-----------------------------|------------------|--------------|---------------------------------|----------------------------------------------------------------------------|
| Plevris 2017 [29] | IBD                       | Center-based cohort study   | Biosimilar infliximab | NR           | Gastrointestinal units, center data | Nine percent of patients switched experienced dose escalation |
| Ratnakumaran 2017 [32] | CD, UC                   | Center-based cohort study   | Biosimilar infliximab | 1 year       | Hospital data                   | Six percent of patients switched experienced dose escalation |
| Rodriguez 2017 [28]  | IBD (CD and UC)          | Center-based cohort study   | Biosimilar infliximab | 1 year       | Hospital data                   | Eleven percent and 13 percent of patients switched had surgery and used steroid after the non-medical switch |
| St. Clair Jones 2017 [31] | IBD (CD and UC)        | Center-based cohort study   | Biosimilar infliximab | 6 months     | Hospital data                   | Of switch patients, 11.3 percent experienced dose escalation and a payment was negotiated to fund the switch |
| Szlumper 2017 [19]  | Rheumatology              | Center-based cohort study   | Biosimilar etanercept | 7 months     | Biologic registry               | Three switchers requested face-to-face consultations on use of delivery device; all potential switchers were invited to face-to-face switching clinic with specialist pharmacist and nurse |
| Barnes 2018 [23]    | RA, AS, PA                | Interview                   | Biosimilar etanercept | NR           | Interview                       | Staff spent 320–1076 additional hours on the non-medical switch across the four centers |
| Citations      | Diseases       | Study type            | Biosimilar       | Time horizon | Data source                             | Reported HRU                                                                                                                                                                                                 |
|----------------|----------------|-----------------------|------------------|--------------|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Glintborg 2018 | RA, PA, AS     | Registry/National database | Biosimilar infliximab | 1 year       | DANBIO, Danish National Patient Registry | The included patients had 39 more outpatient visits within 6 months after the switch than before. Total days with services were 4131 before (mean 5.4 days, SD 2.8) and 4400 after switch (mean 5.8 days, SD 2.8) \((p < 0.01, \text{ paired } t \text{ test})\). After the switch, 259 patients (34%) had fewer (mean \(-2.4\), SD 1.7), 169 patients (22%) had the same and 341 patients (45%) (mean 2.6, SD 2.0) had more days with services than before switch. Patients on average had more phone consultation (1.17 vs. 1.03, \(p = 0.03\)), patient guidance (0.49 vs. 0.35, \(p < 0.01\)), intravenous medication (0.11 vs. 0.03, \(p < 0.01\)), clinical investigation (0.47 vs. 0.31, \(p < 0.01\)), clinical control (2.26 vs. 2.08, \(p < 0.01\)) and observation (0.22 vs. 0.17, \(p < 0.01\)) within 6 months after switch. |
| Nisar 2018     | RA             | Center-based cohort study | Biosimilar rituximab | 1 year       | Hospital data                          | Two patients (8%) experienced emergency department visits after switching. 5 (20%) had severe serum sickness reaction within the 1st week of the second dose and lost response. Four (17%) requested to return to the originator. |
| Citations          | Diseases       | Study type           | Biosimilar         | Time horizon | Data source                           | Reported HRU                                                                                           |
|--------------------|----------------|----------------------|--------------------|--------------|---------------------------------------|--------------------------------------------------------------------------------------------------------|
| Peral 2018 [20]    | RA             | Simulation study     | Biosimilar etanercept | 1 year       | DANBIO registry, survey of 30 rheumatologists in Spain | The non-medical switch is associated with treatment adjustment costs, including monitoring, hospitalization and other healthcare costs |
| Rodriguez 2018 [26]| CD, UC, AS, RA | Center-based cohort study | Biosimilar infliximab | 11 months    | Hospital data                         | One patient required treatment intensification; a total of four patients required an increased dose of immunomodulatory drugs |
| Shah 2018 [21]     | RA             | Center-based cohort study | Biosimilar etanercept | 1 year       | Hospital data                         | For RA patients treated with high intensity etanercept to switch to etanercept biosimilar, 2 days of pharmacists’ time were required per week for 6 months, costing about €22,294 |
| Zahorian 2018 [22] | IBD (CD and UC)| Center-based cohort study | Biosimilar infliximab | NR           | Pharmacists’ experience and hospital data | Pharmacists spent an average of 5–10 min on the phone per patient providing education and answering questions to assist the switching process |

AS ankylosing spondylitis, CD Crohn’s disease, HRU healthcare resource utilization, IBD inflammatory bowel disease, NMS non-medical switch, NR not reported, PA psoriatic arthritis, RA rheumatoid arthritis, SD standard deviation, UC ulcerative colitis
| Citations         | Diseases                                         | Study type                        | Time horizon | Switch population<sup>a</sup> | Drug costs (total €)                                      | Annualized drug costs<sup>a</sup> (€/person/year) |
|------------------|--------------------------------------------------|-----------------------------------|--------------|-------------------------------|----------------------------------------------------------|--------------------------------------------------|
| Jha 2015 [47]    | RA, AS, IBD (CD and UC), PsO, PA                 | Simulation study                  | 1 year       | 3,750,611                     | 3.0–34.5 million cost reduction                           | 7–21 cost reduction                               |
| Bocquet 2016 [51]| Gastroenterology, rheumatology, dermatology and others | Simulation study                  | 1 year       | 5483                          | 20% discount: 7.8 million cost reduction                  | 20% discount: 1427 cost reduction                  |
|                  |                                                   |                                   |              |                               | 30% discount: 11.7 million cost reduction                 | 30% discount: 2141 cost reduction                  |
| Shah 2016 [53]   | RA                                              | Simulation study                  | 1 year       | 7343                          | Infliximab: 37,115,928 cost reduction                    | Infliximab: 5055 cost reduction                    |
|                  |                                                   |                                   |              |                               | Adalimumab: 28,599,516 cost reduction                    | Adalimumab: 3895 cost reduction                    |
| Dyball 2017 [36] | RA                                              | Center-based cohort study         | NR           | 38                            | 29,428 cost reduction                                   | 774 cost reduction                                |
| Gomez 2017 [56]  | Rheumatology, dermatology, gastroenterology     | Simulation study                  | 1 year       | 326                           | 784,270 cost reduction                                  | 2406 cost reduction                                |
| Ratnakumaran 2017 | IBD (CD and UC)                                 | Center-based cohort study         | 1 year       | 191                           | > 1.11 million cost reduction                            | > 5812 cost reduction                              |
| Razanskaite 2017 | IBD (CD and UC)                                 | Center-based cohort study         | 1 year       | 143                           | 565,905–848,858 cost reduction                          | 3957–5936 cost reduction                          |
| Rodriguez 2017   | IBD (CD and UC)                                 | Center-based cohort study         | 1 year       | 72                            | 248,716 cost reduction                                  | 3454 cost reduction                                |
| Garcia-Fernandez 2018 [58] | Gastroenterology, rheumatology, dermatology and other diseases | Center-based cohort study     | 8 months     | 76                            | 62,692 cost reduction                                   | 1237 cost reduction                                |
| Husereau 2018 [42]| IBD (CD)                                        | Simulation study                  | 10 years     | NR                            | 31,042 cost reduction                                   | 3104 cost reduction                                |
| Citation    | Diseases                       | Study type          | Time horizon | Switch population | Drug costs (total €) | Annualized drug costs (€/person/year) | Drug costs (total €) | Annualized drug costs (€/person/year) |
|-------------|--------------------------------|---------------------|--------------|-------------------|---------------------|----------------------------------------|---------------------|--------------------------------------|
| Mora 2018 [61] | Gastroenterology and dermatology | Center-based cohort study | 1 year       | 10                | Total: 38,237 cost reduction | Overall average: 3824 cost reduction | Gastroenterology: 25,037 cost reduction | Dermatology: 13,200 cost reduction |
| O’Brien 2018 [62] | IBD                           | Center-based cohort study | 8 months     | 20                | 15–45% discount on biosimilar price: 77,953–183,189 cost reduction | 15% discount on biosimilar price: 5846 cost reduction | 45% discount on biosimilar price: 13,739 cost reduction |
| Rodriguez 2018 [26] | IBD (CD and UC), RA, and AS | Center-based cohort study | 11 months    | 48                | 73,476 cost reduction | 1670 cost reduction | 26,4% cost reduction |
| Shah 2018 [21] | RA                            | Center-based cohort study | 1 year       | 151               | 557,350 cost reduction | 120,985,327 cost reduction | 100,000 cost reduction |
| Jha 2015 [46, 47] | IBD (CD and UC)               | Simulation study     | 1 year       | NR                | Switch population incurred cost reduction | CD 07–164 million | UC 03–54 million |
| Citations       | Diseases                          | Study type     | Time horizon | Switch population | Drug costs (total €) | Annualized drug costs (€/person/year) |
|-----------------|-----------------------------------|----------------|--------------|-------------------|----------------------|-----------------------------------------|
| Sun 2015 [65]   | Breast cancer, DLBCL              | Simulation     | 14 days      | 10,000            | 10%, 20%, 30%, 40%, 100% conversion rate, annual cost reductions 1.5, 3, 4.5, 6, 7.5, 15 million | NA                                      |
| Bhattacharyya   | RA and PsO                         | Simulation     | 1 year       | 27,052            | 5.7–16.9 million cost reduction | NA                                      |
| 2016 [50]       |                                   |                |              |                   |                      |                                         |
| Claus 2016 [70] | All authorized indications        | Simulation     | 5 years      | NR                | 20% switch: Infliximab: 772,630 cost reduction Filgrastim: 106,895 cost reduction Follitropine alfa: 19,598 cost reduction Epoetin alfa: 7469 cost reduction 100% switch: Infliximab: 7,910,767 cost reduction Filgrastim: 534,474 cost reduction Follitropine alfa: 97,988 cost reduction Epoetin alfa: 37,343 cost reduction | NA                                      |
| Trancart 2016   | RA                                | Simulation     | 3 years      | 45,903            | 28.9 million cost reduction | NA                                      |
| [54]            |                                   |                |              |                   |                      |                                         |
| Citations       | Diseases                                                   | Study type             | Time horizon   | Switch population<sup>a</sup> | Drug costs (total €)                                                                 | Annualized drug costs (€/person/year) |
|-----------------|------------------------------------------------------------|------------------------|----------------|-------------------------------|--------------------------------------------------------------------------------------|----------------------------------------|
| Alexandre 2017  | RA                                                         | Simulation study       | 5 years        | 943–1571                      | 4.1–6.9 million cost reduction                                                      | NA                                     |
| [55]            |                                                             |                        |                |                               |                                                                                     |                                         |
| McBride 2017    | Chemotherapy-induced (febrile) neutropenia                 | Simulation study       | 5, 7, 11, 14 days | 20,000                        | Cost reduction per cycle of filgrastim-sndz over filgrastim                          | NA                                     |
| [67]            |                                                             |                        |                |                               | 5 days: 6,263,133                                                                  |                                         |
|                 |                                                             |                        |                |                               | 7 days: 8,768,386                                                                  |                                         |
|                 |                                                             |                        |                |                               | 11 days: 879,435,766                                                              |                                         |
|                 |                                                             |                        |                |                               | 14 days: 17,536,772                                                                |                                         |
| [68]            |                                                             |                        |                |                               |                                                                                     |                                         |
| McBride 2017    | Chemotherapy induced neutropenia                           | Simulation study       | 1–14 days      | 20,000                        | 6.2–17.6 million cost reduction                                                      | NA                                     |
| [66]            |                                                             |                        |                |                               |                                                                                     |                                         |
| McBride 2017    | Chemotherapy-induced (febrile) neutropenia prophylaxis     | Simulation study       | Chemotherapy of 1 or 6 cycles | 20,000                       | Biosimilar vs. Neupogen: 164–2158 cost reduction                                    | NA                                     |
| [66]            |                                                             |                        |                |                               |                                                                                     |                                         |
| Peck 2017       | Multiple myeloma, NHL                                       | Center-based cohort study | 1 year       | 50                             | 2676 cost increase                                                                  | NA                                     |
| [25]            |                                                             |                        |                |                               |                                                                                     |                                         |
| Ravonimbola 2017| Obstetrics/gynecology                                      | Simulation study       | NR             | 100                            | Follitropin Alfa biosimilar 1: 25,900 cost reduction                                | NA                                     |
| [69]            |                                                             |                        |                |                               |                                                                                     |                                         |
|                 |                                                             |                        |                |                               | Follitropin Alfa biosimilar 2: 27,900 cost reduction                                |                                         |
| Citations       | Diseases                     | Study type                        | Time horizon | Switch population<sup>a</sup> | Drug costs (total €) | Annualized drug costs (€/person/year) |
|-----------------|------------------------------|-----------------------------------|--------------|--------------------------------|---------------------|----------------------------------------|
| Reichardt 2017  | NR                           | Simulation study                  | NR           | NR                             | 16,848 cost reduction | NA                                     |
| [71]            |                              |                                   |              |                                |                     |                                        |
| St. Clair Jones | IBD (CD and UC)              | Center-based cohort study         | 6 months     | 71                             | 249,693 cost reduction | NA                                     |
| 2017 [31]       |                              |                                   |              |                                |                     |                                        |
| Szlumper 2017   | Rheumatology                 | Center-based cohort study         | 7 months     | 80                             | 155,947 cost reduction | NA                                     |
| [19]            |                              |                                   |              |                                |                     |                                        |
| Healy 2018 [59] | IBD (Pediatric)              | Center-based cohort study         | 1 year       | 60                             | 278,675–306,543 cost reduction | NA                                     |
| Ma 2018 [60]    | Rheumatology                 | Center-based cohort study         | 6 months     | 50                             | 732,671 cost reduction | NA                                     |

AS ankylosing spondylitis, CD Crohn’s disease, DLBCL diffuse large b-cell lymphoma, IBD inflammatory bowel disease, NHL non-Hodgkin lymphoma, NMS non-medical switching, NR not reported, PA psoriatic arthritis, PsO psoriasis, RA rheumatoid arthritis, r-hFSH recombinant human follicle-stimulating hormone, SA spondylarthritis, UC ulcerative colitis

* Switch population refers to patients who switched from biologic originators to biosimilar
full-text articles, 923 were conference proceedings and five were gray literature publications (Fig. 1). After screening, 54 studies met the inclusion criteria: 12 full-text articles and 42 conference proceedings (Table 1).

**Study Characteristics**

The characteristics of the 54 publications were summarized in Table 1. Of these identified studies, 23 (43%) were budget impact models, simulations or cost calculation studies; 26 (48%) were medical center-based cohort studies; 3 (6%) were national database analyses; 1 (2%) was an interview study; 1 (2%) was a policy review. Infliximab biosimilar was most commonly reported (n = 26; 48%), followed by etanercept biosimilar (n = 12; 22%) and granulocyte-colony-stimulating factor (G-CSF) biosimilar (n = 5; 9%). Studies of other biosimilars were less frequent, including erythropoiesis-stimulating agent (ESA) biosimilars (n = 2; 4%), adalimumab biosimilar (n = 1, 2%), follicle-stimulating hormone (FSH) biosimilar (n = 1, 2%), rituximab biosimilar (n = 1, 2%) and somatropin biosimilar (n = 1; 2%); two studies (4%) included multiple biosimilars; three studies (6%) did not report which particular biosimilar(s) were studied.

Most of the studies focused on rheumatology, dermatology or gastroenterology (n = 40; 74%), followed by various types of cancer including non-Hodgkin lymphoma (NHL), multiple myeloma, colorectal and breast cancer (n = 6; 11%). Studies in other therapeutic areas were rather sporadic, including hemodialysis (n = 1; 2%), pediatric growth disturbances (n = 1; 2%) and obstetrics/gynecology (n = 1; 2%); five studies (9%) did not report a specific disease area. Depending on the study type, the time horizon and total sample size of the identified publications varied substantially, ranging from 1 day to 5 years and from 18 to 3,750,611 patients, respectively.

**POST-NMS HRU AND HRU-RELATED COSTS**

Seventeen studies reported real-world HRU or HRU-related costs (Table 2). Among them, three were national database studies (two in Denmark [16, 17] and one in Turkey [18]) and all of these three studies reported higher HRU and HRU-related costs after NMS than before NMS based on observed data. The Denmark study enrolled 769 patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis and reported that patients on average had 5.4 outpatient visits in the 6 months before NMS and 5.7 outpatient visits after NMS from infliximab originator to biosimilar (p = 0.0003) [16]. An update of the Denmark study reported 39 more outpatient visits within 6 months after NMS in the same population. In addition, patients on average had more phone consultations (1.17 vs. 1.03, p = 0.03), patient guidance (0.49 vs. 0.35, p < 0.01), intravenous medication (0.11 vs. 0.03, p < 0.01), clinical investigation (0.47 vs. 0.31, p < 0.01), clinical control (2.26 vs. 2.08, p < 0.01) and observation (0.22 vs. 0.17, p < 0.01) within 6 months after switch though the immediate cost consequences of NMS were not substantial [17]. The Turkey study focused on costs and reported that inpatient costs were €9 per patient 1 year before NMS and €21 per patient per year after NMS (p = 0.313); outpatient costs were €58 per patient 1 year before NMS and €87 per patient per year after NMS (p < 0.01); pharmacy costs were €428 per patient 1 year before NMS and €474 per patient per year after NMS (p = 0.371); the total healthcare costs were €528 per patient 1 year before NMS and €647 per patient per year after NMS, an average increase of €119 (23%) per patient per year (p = 0.046) [18].

Thirteen medical center-based cohort studies reported post-NMS treatment costs or medical services (Table 2). Specifically, these studies reported more NMS consultations and outpatient visits [17, 19–23], post-NMS visits or phone consultations for patients experiencing injection-site pain [24], post-NMS medication usage [17, 25, 26], post-NMS loss of response and emergency department visit [27], post-NMS surgery rate (11%) [28], post-NMS steroid use (13%) [28] and post-NMS biosimilar dose escalation (6–35.4%) [26, 29–32]. Nine reported patients discontinued the biosimilar and
switched back to the originator [24, 27, 29, 31, 33–37]. In addition, semi-structured one-on-one interviews among staff members involved in an NMS of the originator etanercept to its biosimilar at four rheumatology centers in the UK reported that providers spent 320–1076 additional hours on the NMS process for 149–180 patients per center [38].

NMS-Related Drug, Healthcare and Management Costs

A total of 48 studies estimated NMS-related costs, including 32 estimating drug cost only, 10 estimating healthcare cost without specifying a detailed breakdown, 1 reporting both drug and unspecified healthcare costs and 5 estimating NMS setup and managing costs. Among these studies, only the Turkey registry study reported observed real-world total healthcare costs as well as HRU-related costs that were summarized previously (Table 2).

For the 33 studies reporting post-NMS expected drug cost reduction, 18 were simulation or modeling studies and 15 were center-based cohort studies (Table 3). The drug cost reduction was estimated to range from €164 to €879 million over different sizes of switch populations and varying lengths of follow-up. Considering the substantial variations in study designs, sample size and duration of follow-up, annualized post-NMS drug cost reductions were calculated for 15 studies with a follow-up period > 1 year and available cohort size, resulting in €7 to €13,739 per patient per year (Table 4).

Among the five studies estimating NMS setup and managing costs, one modeling study expected cost increases related to NMS planning activities ranging from €14,088 to €17,028 and NMS management from €7775 to €68,427 per medical center [38]. One simulation study reported an estimated short-term cost increase of €21,867 per medical center for the NMS program and subsequent administrative support from the perspective of rheumatology centers in the UK [39]. Additionally, an overall cost associated with the switching process was estimated to be €2358 per person, including €106 for patient selection and contracting based on a budget impact model from a UK perspective [40]. Another simulation study reported the estimated short-term NMS costs of €57.48 per patient from the perspective of providers in the US [41]. Finally, an interview study [23] reported NMS costs associated extra staff time. The per-person NMS cost needed to pay healthcare practitioners ranged from €217 to €448.

DISCUSSION

As more biosimilars are introduced into the market worldwide, biosimilar NMS uptake is expected to increase because of the perceived potential cost reduction from a discounted drug price. However, biosimilar medications are approved under the premise of biosimilarity rather than interchangeability. While continued efforts are made to evaluate clinical outcomes associated with biosimilar NMS (e.g., development of anti-drug antibody, immunogenic response in the context of immunosuppressant therapy), it has become increasingly important to understand the real-world
economic impact of biosimilar NMS on HRU and costs from a holistic perspective beyond drug price.

Furthermore, the market pertaining to originator biologics and biosimilars is volatile under the current economic and political climate worldwide. The future of the relationship...
| Table 4 | Annualized cost difference between post- and pre-NMS |
|---------|-------------------------------------------------------|
| Citations | Diseases | Study type | Biosimilar | Time horizon (N) | Switch population | Cost difference after vs. before NMS |
| Phillips 2017 [18] | All authorized indications | Registry/National database | Biosimilar infliximab | 1 year | 136 | Cost increase per patient |
| Phillips 2017 [18] | Diseases | Observation study | Biosimilar etanercept | 1 year | NR | Cost increase per patient |
| Peral 2018 [20] | RA | Simulation study | Biosimilar infliximab | 1 year | 98 | Cost increase per patient |
| Fleischmann 2013 [24] | Pediatric growth disturbances | Center-based cohort study | Biosimilar etanercept | About 3 years | 21 | Cost increase per patient |
| Ala 2016 [48] | IBD (CD) | Center-based cohort study | Biosimilar infliximab | 6 months | 88 | Cost increase per patient |
| Rahmanny 2016 [52] | IBD (CD and UC) | Center-based cohort study | Biosimilar infliximab | 6 months | 25 | Cost increase per patient |
| Sheppard 2016 | Rheumatology | Center-based cohort study | Biosimilar infliximab | 1 year | NR | Cost increase per patient |
| Plevris 2017 [29] | IBD (CD and UC) | Center-based cohort study | Biosimilar infliximab | 7 months | 80 | Cost increase per patient |
| Salumper 2017 | Rheumatology | Center-based cohort study | Biosimilar infliximab | 3 months | 17 | Cost increase per patient |
| Salumper 2017 | PsO | Center-based cohort study | Biosimilar etanercept | 6 months | 50 | Cost increase per patient |
| Ma 2018 [60] | Rheumatology | Center-based cohort study | Biosimilar etanercept | About 3 years | 21 | Cost increase per patient |

*Anticipated annual cost difference per patient (€/person/year)*

| Phillips 2017 [18] | 119,000 cost increase per patient |
| Phillips 2017 [18] | 305,326 cost reduction |
| Phillips 2017 [18] | 749,437 cost reduction |
| Peral 2018 [20] | 730,000 cost increase per patient |
| Phillips 2017 [18] | 82,528 cost reduction |
| Phillips 2017 [18] | 791,437 cost reductions |
| Phillips 2017 [18] | 155,947 cost reductions |
| Phillips 2017 [18] | 154,492 cost reductions |
| Phillips 2017 [18] | 174,628 cost reductions |
between originators and biosimilars may be reshaped for factors such as prices and accesses that are still evolving. To the extent possible, this systematic literature review focused on the economic impact such as HRU and costs related to biosimilar NMS over the past 10 years. The review of the economic implications of biosimilar NMS found more data on the anticipated post-NMS cost estimates than on the real-world observed post-NMS costs or HRU. There were also more simulation studies on NMS implications due to drug acquisition costs rather than providing costs estimates comprised of all health care services required during and after NMS. In fact, observed real-world HRU and/or HRU-related costs with a sufficient follow-up period were only reported in three studies using national registry databases. Because biosimilars are not identical copies of their originator biologics, drug price should not be the only determining factor when assessing the economic impact of NMS, unlike the case of small-molecule drug generics [42]. Long-term observations of all healthcare service needs during the post-NMS period could provide a more comprehensive evaluation of the economic impact of NMS. Although existing clinical trials demonstrated similar efficacy and safety of the approved biosimilars, variation exists when it comes to individual patients or specific medical conditions. Monitoring and trial-and-error adjustments are common for any medication switching (including those due to medical reasons such as loss of response). In the situation of NMS, some patients may respond differently to a biosimilar than its originator and potentially generate additional NMS-related costs. For example, after NMS, patients could require additional trial-and-error dosing adjustments and may necessitate additional laboratory tests or follow-up visits to monitor post-NMS status.

In addition, physicians, nurses, patients and healthcare administrators may need to be trained to educate patients on biosimilar NMS, offering support if NMS-related questions from these patients come up and following up with proper monitoring after the initiation of NMS; new administrative procedures may also need to be put in place to initiate, process and

| Table 4 continued |
|---|

| Citations | Diseases | Study type | Biosimilar | Time horizon | NMS Switch population | Cost difference after vs. before NMS | Cost types or components considered were not defined or reported from the included studies. For studies specified the associated population size and time frame to the reported cost difference, annualized and personalized cost differences were imputed. |
|---|
| Healy 2018 [59] | IBD (Pediatric) | Center-based cohort study | Biosimilar infliximab | 1 year | 60 | 278,675–306,543 cost reductions | Costs or components considered were not defined or reported from the included studies. For studies specified the associated population size and time frame to the reported cost difference, annualized and personalized cost differences were imputed. |
| --- |

AS ankylosing spondylitis, CD Crohn’s disease, DLBCL diffuse large b-cell lymphoma, IDI inflammatory bowel disease, NHL non-Hodgkin lymphoma, NMS non-medical switching, RA rheumatoid arthritis, r-hFSH recombinant human follicle-stimulating hormone, SA spondyloarthritis, UC ulcerative colitis

Switch population refers to patients who switched from biologic originators to biosimilar
reimburse the biosimilar. All these activities are likely to generate additional costs due to biosimilar NMS. In two recent modeling studies, over a 3-month period, biosimilar NMS in patients with autoimmune diseases was estimated to increase healthcare costs for both payers and providers, mostly due to extra time needed during office visits and additional laboratory tests, procedures and follow-up visits [39, 41]. While additional monitoring and administrative costs may be partially absorbed by biosimilar manufacturers or healthcare providers, the cost amount may increase over time if a patient underwent more than one NMS because of lack of response, low treatment adherence or adverse events. As a result, in cases of multiple NMS, these seemingly one-time costs may become long-term costs that patients and payers need to bear, likely reducing the NMS cost reduction associated with the lower drug costs of biosimilars.

It is unclear whether rebates or patient support programs for biologic originators were accounted for when studies evaluated drug cost differences between biologic originators and biosimilars. According to one study identified during our literature review, rebates for some originators can already reach up to 50% of their list price, which could result in a similar or even lower price range of its biosimilar [43]. It is also uncertain whether savings to payers, because of the reduced drug price, may be translated to savings for patients if the biosimilar manufacturers do not offer or offer a less generous copayment assistance program.

Besides economic data, to assuage any concerns that patients and physicians may have, more real-world clinical data on the safety and effectiveness of biosimilars compared with their originator biologics are also needed for the short and long term and across indications. Debates on this topic remain. For instance, a recent systematic literature review of post-NMS clinical outcomes suggests that the risk of immunogenicity-related safety issues or diminished efficacy is similar before and after NMS based on a limited number of real-world studies pertaining to the safety of NMS [13]. On the contrary, concerns were raised for the lack of sufficient evidence to support the safety and efficacy of NMS at least for some biosimilars [42]. In the present review, we found that, among the limited real-world studies, after NMS, higher rates of surgery, concomitant medication use, biosimilar discontinuation, switch back to the originator biologic or switch to other biologics were reported. It should be noted that the results of this literature review are consistent with a recent assessment made by Husereau et al. [42] that existing data are insufficient for payers and health technology assessment (HTA) agencies to make decisions regarding biosimilar NMS.

Limitations

This study is subject to some limitations. As with any systematic literature review, the variability in the methodologies used by the identified studies may limit the interpretation and generalizability of the synthesized results. Conducting a meta-analysis and generating a pooled estimate of the impact of NMS on HRU and costs was not possible because of methodologic differences across studies. Furthermore, it should be noted that the skewed proportion of studies considering NMS for the infliximab biosimilar may limit the generalizability of the current results to NMS involving other biologics. We found that switching from the originator infliximab to its biosimilar was most frequently studied, likely because it was one of the first approved biosimilars and several versions are currently on the market in different countries [44, 45]. Indeed, almost half of the identified studies (n = 26; 48%) evaluated the infliximab biosimilar NMS, albeit with substantial variations in study design and estimates of the NMS economic impact. Overall, a limited number of studies evaluated the economic impact of NMS and even fewer had real-world HRU estimation. Among the identified studies, most are conference abstracts. Quality assessment for conference proceedings may have not undergone as thorough a peer-review process as a manuscript published by a journal. No study quality classification was made for this systematic literature review because of the lack of validated instrument for studies analyzing
healthcare costs and HRU. Moreover, the majority of included studies were either abstracts from conference proceedings or simulation studies with heavy assumptions. Future research providing more real-world evidence regarding biosimilar NMS as well as studies developing and validating instruments to evaluate the quality of such studies is warranted.

CONCLUSION

The future concerning originators vs. biosimilars continues evolving and requires close monitoring of this dynamic field. With a focus on the economic impact such as HRU and costs over the past 10 years, this systematic literature review found that the overall economic impact of biosimilar NMS remains uncertain. Drug costs continue to be the sole focus of most modeling and medical center-based studies. Only three real-world database studies reported observed economic consequences of biosimilar NMS with two of them showing an increase in the HRU and costs associated with biosimilar NMS and one suggesting no immediate cost impact. More real-world studies that include both drug costs and other NMS-related medical and administrative costs are needed to quantify the full economic impact of NMS in both the short and long term. In particular, better understanding the upfront costs required to prepare patients and prescribers for biosimilar NMS to manage the expectations (e.g., patient education and support, trainings to healthcare professionals) can be important, which may help mitigate the potential consequences associated with biosimilar NMS. Collectively, this information would allow payers, physicians and policy makers to more comprehensively assess the implications of biosimilar NMS.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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