Health Technology Assessment (HTA)

Scoping Report

Title	Infliximab reference product versus biosimilar for the treatment of rheumatoid arthritis: scoping report
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Technology	Infliximab biosimilars
Date	September 10, 2020
Type of Technology	Pharmaceuticals

Executive Summary:

As patents for first-to-market biologics expire, subsequent-entry products – biosimilars – can become available. Biosimilars are not exact copies of their reference products but highly similar with regard to efficacy and safety and available at a discount. In Switzerland, relatively low biosimilar prescription rates have prompted interest in a health technology assessment (HTA) of the infliximab reference product relative to biosimilars for treating rheumatoid arthritis (RA). This scoping report determines the feasibility of such an HTA.

We conducted a systematic literature search for evidence on efficacy, effectiveness, safety, and health economic outcomes of the infliximab reference product relative to biosimilars in RA. We also conducted a targeted search for evidence on biosimilar-related ethical, legal, social, and organisational aspects.

We identified 15 studies reporting on randomized controlled trials (RCTs), 14 real-world evidence (RWE) studies, and 11 health economic studies. RCTs reported a range of clinical efficacy, safety, pharmacokinetic/pharmacodynamic, immunogenicity, and patient-reported outcomes. RWE studies primarily reported on effectiveness, safety, and treatment discontinuation. Health economic studies were costing studies or budget impact analyses.

A substantial body of literature was identified on biosimilar regulation in different settings. For legal and ethical aspects, we developed sets of questions that we considered important for discussing reference products and biosimilars, particularly with regard to non-medical switching.

The evidence base suggested that an HTA comparing the infliximab reference product with its biosimilars for treatment of RA in infliximab-naïve and switched patients would be feasible. This HTA would have to include a systematic review (and possibly a meta-analysis) of efficacy, effectiveness, and safety as well as a budget impact analysis (but not necessarily a full economic evaluation).

Zusammenfassung:

Wenn die Patente von First-to-Market-Biologika auslaufen, können Folgeprodukte – Biosimilars – verfügbar werden. Biosimilars sind keine genauen Kopien der jeweiligen Referenzprodukte. Jedoch ähneln sie ihnen in Bezug auf Wirksamkeit und Sicherheit stark und werden zu einem günstigeren Preis angeboten. In der Schweiz ist aufgrund relativ niedriger Verschreibungsraten von Biosimilars das Interesse an einem Health Technology Assessment (HTA) des Referenzprodukts Infliximab im Vergleich zu Biosimilars zur Behandlung der rheumatoiden Arthritis (RA) aufgekommen. In diesem Scoping-Bericht wird die Machbarkeit eines solchen HTA erörtert.

Wir haben eine systematische Literaturrecherche betreffend Wirksamkeit, Effektivität, Sicherheit und gesundheitsökonomische Ergebnisse des Referenzprodukts Infliximab im Vergleich zu Biosimilars bei RA durchgeführt. Zudem haben wir eine gezielte Suche nach Erkenntnissen zu ethischen, rechtlichen, sozialen und organisatorischen Aspekten im Zusammenhang mit Biosimilars vorgenommen.

Wir identifizierten 15 Studien, die über randomisierte kontrollierte Versuche (RCT) berichten, 14 Real-World-Evidence-Studien (RWE) sowie 11 gesundheitsökonomische Studien. RCT untersuchten klinische Wirksamkeit, Sicherheit, Pharmakokinetik/Pharmakodynamik, Immunogenität und Patient Reported Outcomes, während sich RWE-Studien überwiegend mit Wirksamkeit, Sicherheit und Behandlungsabbrüchen befassten. Bei den gesundheitsökonomischen Studien handelte es sich um Kostenstudien oder Budget-Impact-Analysen.

Wir fanden umfangreiche Literatur zur Regulierung von Biosimilars in unterschiedlichen Kontexten. Hinsichtlich rechtlicher und ethischer Aspekte haben wir Kataloge von Fragen entwickelt, die wir für die Diskussion von Referenzprodukten und Biosimilars für wichtig erachteten, insbesondere im Hinblick auf das Switching aus nicht-medizinischen Gründen.

Die Evidenzbasis liess darauf schliessen, dass ein HTA, bei dem das Infliximab-Referenzprodukt mit seinen Biosimilars zur Behandlung von RA bei Infliximab-naiven und geswitchten Patienten verglichen wird, machbar ist. Dieses HTA müsste eine systematische Überprüfung (und möglicherweise eine Metaanalyse) der Wirksamkeit, Effektivität und Sicherheit sowie eine Budget-Impact-Analyse (aber nicht zwingend eine vollständige ökonomische Bewertung) umfassen.

Synthèse:

Au fur et à mesure que les brevets de produits biologiques inédits expirent, d'autres produits, dits biosimilaires, peuvent leur succéder. Les biosimilaires ne sont pas des copies exactes de leur produit de référence, mais ils sont aussi sûrs et efficaces, tout en étant vendus à moindres coûts. Le nombre relativement faible de biosimilaires prescrits en Suisse a suscité un intérêt pour une évaluation des technologies de la santé (ETS) comparant l'infliximab, produit de référence, à des biosimilaires dans le traitement de la polyarthrite rhumatoïde (PR). Le présent rapport vise à déterminer si une telle évaluation est faisable.

Nous avons mené une recherche bibliographique systématique pour identifier les preuves de l'efficacité, de la sécurité et de l'incidence sur l'économie de la santé de l'infliximab en comparaison avec des biosimilaires. Nous avons également dirigé nos recherches sur les aspects éthiques, légaux, sociaux et organisationnels liés aux produits biosimilaires.

Nous avons relevé 15 études fondées sur des essais contrôlés randomisés (RCT pour randomised controlled trials), 14 études basées sur des preuves empiriques (RWE pour real-world evidence) et 11 études sur l'économie de la santé. Les RCT abordent l'efficacité clinique, la sécurité, la pharmacocinétique/pharmacodynamique et l'immunogénicité ainsi que des effets signalés par les patients. Les RWE observent principalement l'efficacité, la sécurité et l'arrêt du traitement. Les études d'économie de la santé comprennent des études de coûts et des analyses d'incidence budgétaire.

La littérature concernant la réglementation des biosimilaires dans différents contextes est fournie. En ce qui concerne les aspects légaux et éthiques, nous avons développé des séries de questions que nous considérions importantes pour discuter des produits de référence et de leurs biosimilaires, particulièrement au regard de changements de traitement pour des raisons autres que médicales.

Les preuves suggèrent qu'une ETS comparant l'infliximab, produit de référence, à ses biosimilaires dans le traitement de la PR chez des patients n'ayant jamais pris d'infliximab ou ayant changé de traitement serait faisable. L'évaluation devrait inclure une revue systématique (éventuellement une méta-analyse) de l'efficacité et de la sécurité ainsi qu'une analyse de l'incidence budgétaire (mais pas nécessairement une évaluation économique complète).

Sintesi:

Via via che scadono i brevetti per i primi medicamenti biologici immessi in commercio possono rendersi disponibili prodotti biosimilari commercializzati in un secondo tempo. I biosimilari non sono copie esatte dei loro prodotti di riferimento, ma molto simili per quanto riguarda l'efficacia e la sicurezza e disponibili a costi inferiori. In Svizzera, il numero di prescrizioni relativamente basso di biosimilari ha suscitato interesse per un health technology assessment (HTA) del prodotto di riferimento infliximab in confronto ai suoi biosimilari per il trattamento dell'artrite reumatoide (AR). Questo rapporto di scoping determina la fattibilità di un HTA del genere.

Abbiamo condotto una ricerca bibliografica sistematica sull'efficacia, l'efficienza, la sicurezza e le ripercussioni sull'economia sanitaria del prodotto di riferimento infliximab rispetto ai biosimilari nell'AR. Inoltre abbiamo condotto una ricerca mirata sugli aspetti etici, legali, sociali e organizzativi legati ai biosimilari.

Dalla nostra ricerca sono emersi 15 studi controllati randomizzati (RCT), 14 studi real-world evidence (RWE) e 11 studi di economia sanitaria. Dagli RCT è scaturita una serie di risultati sull'efficacia clinica, la sicurezza, la farmacocinetica/farmacodinamica, l'immunogenicità e gli effetti riferiti dai pazienti. Gli studi RWE hanno fornito soprattutto informazioni sull'efficacia, la sicurezza e l'interruzione del trattamento. Gli studi di economia sanitaria hanno esaminato i costi o analizzato l'impatto sul budget.

È stata identificata una bibliografia sostanziale sul disciplinamento dei biosimilari in diversi contesti. Per gli aspetti legali ed etici abbiamo elaborato serie di domande da noi considerate importanti per la discussione sui prodotti di riferimento e i biosimilari, in particolare per quanto riguarda il cambio di terapia non giustificato da motivi medici.

Le prove raccolte hanno suggerito che un HTA che confronti il prodotto di riferimento infliximab con i suoi biosimilari per il trattamento dell'AR nei pazienti naive all'infliximab e in quelli che cambiano terapia sarebbe fattibile. Questo HTA dovrebbe comprendere un esame sistematico (e possibilmente una meta-analisi) dell'efficacia, dell'efficienza e della sicurezza, nonché un'analisi di impatto sul budget (ma non necessariamente una valutazione economica completa).

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Abbreviations and acronyms

ACPA	Anti-Citrullinated Peptide Antibodies
ACR	American College of Rheumatology
ADAb	Anti-Drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AS	Ankylosing Spondylitis
AxSpA	Axial Spondyloarthritis
B[o/s]DMARD	[Biological Originator/Biosimilar] Disease-Modifying Anti-Rheumatic Drug
CEA	Cost-Effectiveness Analysis
CDAI	Clinical Disease Activity Index
COI	Conflict of Interest
COS	Core Outcome Set
CRP	C-Reactive Protein
csDMARD	Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug
DAS	Disease Activity Index
DMARD	Disease-Modifying Anti-Rheumatic Drug
EEA	European Economic Area
EKO	Erstattungskodex (list of drugs reimbursed by healthcare insurance in Austria)
ELSO	Ethical, Legal, Social, Organizational
EMA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAQ-DI	Health Assessment Questionnaire Disability Index (also just HAQ)
HMG	Heilmittelgesetz (Therapeutic Products Act)
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
IBD	Inflammatory Bowel Disease
IL	Interleukin
INX	Infliximab
IV	Intravenous
KVG	Krankenversicherungsgesetz (Swiss health insurance law)
MA	Meta-Analysis
mAb	Monoclonal Antibody
MHAQ/MDHAQ	Modified/Multidimensional Health Assessment Questionnaire
MTC	Mixed Treatment Comparison
NA	Not Applicable
NMA	Network Meta-Analysis
PD	Pharmacodynamics
PICO	Population, Intervention, Comparator, Outcome
PK	Pharmacokinetics
PROM	Patient-Reported Outcome Measure
PsA	Psoriatic Arthritis
PSO	Psoriasis
RA	Rheumatoid Arthritis
RAID	Rheumatoid Arthritis Impact of Disease
RAPID	Routine Assessment of Patient Index Data
RCT	Randomized Clinical Trial
RWE	Real-World Evidence
SDAI	Simplified Disease Activity Index
SL	Spezialitätenliste (list of drugs reimbursed by mandatory healthcare insurance in Switzerland)

SpA	Spondyloarthritis
SSC	Swiss Supreme Court
TNF	Tumour Necrosis Factor
tsDMARD	Targeted Synthetic Disease-Modifying Anti-Rheumatic Drug
UC	Ulcerative Colitis
UK	United Kingdom
US	United States
VAS	Visual Analog Scale

Objective of the HTA scoping report

The objective of the scoping report is to conduct a systematic literature search and to synthesize the available evidence base addressing the main health technology assessment (HTA) domains, i.e., clinical effectiveness/safety, costs/budget impact/cost-effectiveness, legal/social/ethical and organisational issues. In the report, the methods that are to be used when an HTA is pursued are described. Based on quantity and quality of the extracted evidence, the feasibility of pursuing an HTA is judged. Analysis of the individual study outcomes is not the objective of the scoping report.

1 Policy question and context

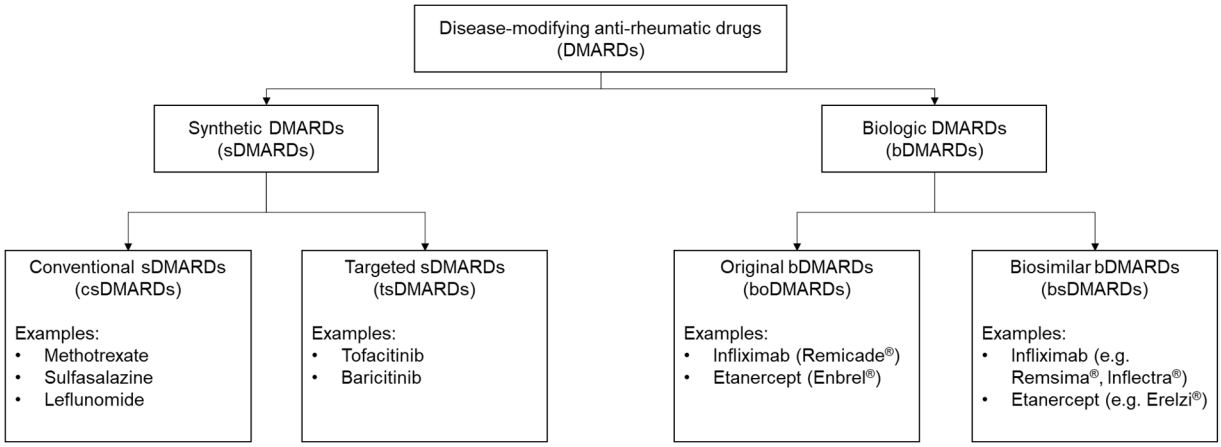
The biopharmaceutical infliximab is a monoclonal antibody (mAb) used to treat a number of inflammatory autoimmune diseases including rheumatoid arthritis (RA). In 2016, infliximab generated costs of around CHF 128 million, rendering it the most cost-incurring drug reimbursed by the mandatory health insurance in Switzerland.[1] For biopharmaceuticals such as infliximab, biological products having sufficient similarity with their previously approved reference product are available as biosimilars. At their market entry, biosimilars have to be at least 25% cheaper than their reference product in order to be reimbursed in Switzerland.[2] In 2018, infliximab biosimilars only accounted for less than 10% of all infliximab prescriptions in Switzerland (Tarifpool: ©SASIS AG; Datenaufbereitung: ©COGE). In contrast, other European countries (such as Norway, Denmark, France, England, the Netherlands and Portugal) exhibit considerably higher proportions of prescribed infliximab biosimilars as these countries adopted policies recommending the substitution of infliximab reference products with biosimilars.[3] These policies are based on clinical studies suggesting that initiating treatment with infliximab biosimilars[4 5] as well as switching patients from infliximab reference product to biosimilars[6 7] is an effective and safe way to treat RA. Therefore, the applicant suggests that an HTA should be performed to evaluate whether initiating treatment with infliximab biosimilars as well as switching patients from infliximab reference product to biosimilars is an effective, safe and cost-effective way to treat RA.

2 Research questions

This scoping report reviewed the evidence base on the safety, clinical efficacy and cost-effectiveness of the infliximab reference product relative to infliximab biosimilar in patients with RA who did not respond adequately to standard therapy with disease-modifying anti-rheumatic drugs (DMARDs).Note that we chose to label the reference product as the intervention and biosimilars as the comparator in line with the target of the Swiss HTA programme, namely disinvestment: Disinvestment would likely target reference products so, as per the FOPH's suggestion, the reference product was treated as the intervention.

The term "standard therapy" was chosen for consistency with infliximab entries in the Spezialitätenliste (SL; the list of drugs reimbursed by mandatory healthcare insurance in Switzerland). Standard therapy, for the purpose of this report, refers to first-line therapy with conventional synthetic DMARDs (csDMARDs), such as methotrexate, leflunomide, or sulfasalazine, and short-term glucocorticoids (see Section 3.2.2).[8–10] Note that we followed the DMARD nomenclature by Smolen *et al.* (Figure 1).[11]

Figure 1 Nomenclature of disease-modifying anti-rheumatic drugs



Source: Developed based on Smolen *et al.*[11]

The following research questions, which informed the development of Population, Intervention, Comparator, Outcome (PICO) criteria (Section 5), were considered:

- Is it safe, clinically efficacious and cost-effective to **initiate** treatment with infliximab biosimilar instead of the infliximab reference product in patients with RA and inadequate response to standard therapy with DMARDs?
- Is it safe, clinically efficacious and cost-effective to **switch** treatment from the infliximab reference product to infliximab biosimilar in patients with RA and inadequate response to standard therapy with DMARDs?

- Is it safe, clinically efficacious and cost-effective to **switch** treatment from infliximab biosimilar to the infliximab reference product in patients with RA and inadequate response to standard therapy with DMARDs?

3 Medical background

3.1 Description of rheumatoid arthritis

Rheumatoid arthritis is a chronic, inflammatory autoimmune disease that puts a substantial burden on patients, healthcare systems, and society.[12 13] The disease mainly affects joints and leads to painful swelling, erosive damage, and functional deterioration. RA can also have extra-articular effects, e.g. on the pulmonary, ocular, vascular, and cardiac systems, so is also referred to as a syndrome with multiple sub-diseases.[12 14]

In this section, we describe the pathophysiology (Section 3.1.1), the aetiology and natural disease course (Section 3.1.2), and the diagnosis/classification and assessment of RA (Section 3.1.4). Subsequent sections describe the treatment (Section 3.2), and the epidemiology and burden of RA (Section 3.3).

3.1.1 Pathophysiology: inflammation and autoimmune response

Multiple inflammatory cascades are involved in RA.[14 15] An important cascade is mediated by the proinflammatory cytokines tumour necrosis factor (TNF) and interleukin (IL) 6 and causes synovial inflammation. Synovial-like fibroblasts, macrophages, and T and B lymphocytes interact and lead to TNF overproduction, which in turn triggers overproduction of IL 6 and other cytokines.[14] Cytokines (and chemokines) in the synovial compartment activate endothelial cells and attract immune cells, which promotes the inflammatory response. The presence of activated fibroblasts, T and B cells, monocytes, and macrophages eventually results in osteoclast activation and differentiation, with subsequent bone erosion.[12 15]

In addition to inflammation, certain autoimmune processes are characteristic for RA. Key autoantibodies include rheumatoid factor, which targets immunoglobulin G, and anti-citrullinated peptide antibodies (ACPA), which bind to citrullinated proteins.[12 14] At least one of these autoantibodies is present in 50 to 80% of patients, and seropositive patients tend to have more severe disease, poorer clinical outcomes, and increased mortality relative to seronegative patients.[12 14]

3.1.2 Risk factors for rheumatoid arthritis

The risk of developing RA is associated with genetic as well as environmental and lifestyle factors. A family history of RA is associated with an increased risk of developing RA, and several genetic loci have

been linked to development of RA.[13 14] Environmental and lifestyle factors consistently linked to RA include smoking and exposure to silica.[13 16 17]

3.1.3 Natural course of rheumatoid arthritis

Development of RA has been described as a result of "multiple hits"[12]: A genetically susceptible person, exposed to environmental triggers and with lifestyle risk factors in conjunction with epigenetic modifications, may lose tolerance to self over time, which leads initially to asymptomatic synovitis and then to symptomatic arthritis.[12 13]

3.1.4 Diagnosis/classification criteria for rheumatoid arthritis

Rheumatoid arthritis is a clinical diagnosis, which is partly based on the exclusion of other diseases: Tender and swollen joints, morning joint stiffness, and increased CRP and erythrocyte sedimentation rate (ESR) levels are typical for RA, but these symptoms could also indicate other forms of arthritis.[12]

Sets of classification criteria are generally used to define RA for study recruitment and comparison of patient populations across studies.[12 18] Classification criteria have changed over time. The 1987 classification criteria proposed by the American Rheumatism Society, for example, were developed to achieve improved sensitivity and stricter definition of RA than in guidelines from the 1950s and 1960s.[19] The 2010 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) criteria in turn were developed to improve upon the sensitivity of the 1987 criteria and identify patients at earlier disease stages, given increasing evidence on the benefits of early treatment initiation.[18 20]

The 2010 ACR/EULAR criteria (Table 1) are applied if synovitis is confirmed in at least one joint for which no other disease provides a plausible explanation. A patient achieving a summary score of at least 6 is classified as having definite RA. Patients presenting at a later stage in their disease can also be classified as having definite RA if they have typical erosions or long-standing disease that would have previously fulfilled the criteria.

Table 1 ACR/EULAR 2010 criteria for classification of rheumatoid arthritis

Classification criteria	Score
Joint involvement	
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3

Classification criteria	Score
>10 joints (at least 1 small joint)	5
Serology (at least one test result needed for classification)	
Negative rheumatoid factor and negative ACPA	0
Low-positive rheumatoid factor or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute phase reactants (at least one test result needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
<6 weeks	0
≥6 weeks	1

Source: Adapted from Aletaha *et al.*[18]
Abbreviations: ACPA, Anti-citrullinated Peptide Antibody; ACR; American College of Rheumatology; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; EULAR; European League Against Rheumatism.
Note: Patients who show typical erosions and/or long-standing disease who would have previously fulfilled these criteria should also be classified as having RA.

3.1.5 Assessment of disease activity and progression

Once patients start treatment, monitoring and regular disease assessment are important to evaluate progress towards treatment targets (see Section 3.2).[21] A range of assessment instruments are available, including laboratory and imaging data and physician- or patient-reported outcomes (PROMs) (see Table 2, which contains the most frequently used measures and those recommended by an ACR working group in their 2019 update).[21] For more information, also on feasibility of assessments, we refer the interested reader to the ACR working group review paper[21] and the ACR website on disease activity and functional status measurement, which provides forms and calculators for key disease activity measurements[22].[21]

Many of these instruments are used as outcomes in efficacy and effectiveness studies of RA treatment, with seven instruments included in a Core Outcome Set (COS) for clinical trials in RA: pain, patient global assessment, physician global assessment, physical disability, swollen joints, tender joints, and acute phase reactants, with radiographic assessment also to be performed in studies of at least 1 year duration.[23 24]

These core outcomes are combined into composite indices to assess disease activity. The most frequently used index is the Disease Activity Index 28 (DAS28, based on assessment of 28 joints).[12 14 25] As the DAS28 is somewhat complex to calculate, simpler indices have been developed, e.g. the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI).[26] Cut-off points have been defined in the literature for these composite indices to classify patients as being in remission or having low, moderate, or high disease activity (low disease activity or remission are established treatment targets in RA (see Section 3.2)).[8 12 27]

Composite indices that assess disease activity based on PROM also exist. Examples include the Patient Activity Scale, the Routine Assessment of Patient Index Data, and the Rheumatoid Arthritis Impact of

Disease (RAID) score.[21 28–30] In general, PROMs, which include the composite indices just listed but also functional status, pain, health-related quality of life (HRQoL), and fatigue, are becoming increasingly important in RA treatment.[31] These measures provide not only valuable information to physicians but also a patient perspective on disease and treatment which may contribute to improve (shared) decision-making in treatment.[32]

Some indices have been designed primarily for use in research. These indices assess change from baseline. Examples include the EULAR response criteria, which use follow-up DAS28 and change in DAS28 to classify disease response as “good”, “moderate”, or “no (response)”, and the ACR response criteria, which specify an improvement of at least a certain magnitude in tender and swollen joint counts and in at least three (of five) additional criteria (Table 2).[33 34]

In addition to assessments of disease activity, radiologic damage should be examined.[14 35] A range of instruments is also available to assess extra-articular manifestations of rheumatoid arthritis (for an overview, see Scott *et al.*[14]).

Table 2 Rheumatoid arthritis assessment instruments

Assessment	Instrument/components	Cut-off points
RA COS assessments		
Acute phase reactant	C-reactive protein (CRP)[36]	—
Acute phase reactant	Erythrocyte sedimentation rate (ESR)[36]	—
Joint count	Tender joint count[37]	—
Joint count	Swollen joint count[37]	—
Patient global assessment	Usually measured with single question on VAS from 0–10 or 0–100[38]	—
Pain	Measured using VAS or numeric, multidimensional, verbal rating scales[39]	—
Physician global assessment	Usually measured on VAS from 0–10[40]	—
Functional status	Frequently measured using HAQ-DI (also known just as HAQ) or its derivatives, e.g. HAQ-II, MHAQ and MHDAQ[28 36 41]	—
Composite indices		
Disease activity	DAS28 (also DAS28-ESR)[42 43] • Tender joint count (of 28) • Swollen joint count (of 28) • ESR (mm) • Global health	• Remission: DAS28<2.6 • Low disease activity: 2.6≤DAS28 ≤3.2 • Moderate disease activity: 3.2<DAS28 ≤5.1 • High disease activity: DAS28>5.1
Disease activity	DAS28-CRP[12 14] • Tender joint count (of 28) • Swollen joint count (of 28) • CRP (mg/dL) • Global health	• Remission: DAS28<2.6 • Low disease activity: 2.6≤DAS28≤3.2 • Moderate disease activity: 3.2<DAS28≤5.1 • High disease activity: DAS28>5.1
Disease activity	Simplified Disease Activity Index (SDAI)[26 42 44] • Tender joint count (of 28) • Swollen joint count (of 28) • CRP (mg/dL) • Patient global assessment (cm) • Physician global assessment (cm)	• Remission: SDAI≤3.3 • Low disease activity: 3.3<SDAI≤11 • Moderate disease activity: 11<SDAI≤26 • High disease activity: SDAI>26
Disease activity	Clinical Disease Activity Index (CDAI)[26 42] • Tender joint count (of 28) • Swollen joint count (of 28) • Patient global assessment (cm) • Physician global assessment (cm)	• Remission: CDAI≤2.8 • Low disease activity: 2.8<CDAI≤10 • Moderate disease activity: 10<CDAI≤22 • High disease activity: CDAI>22

<table>
<tr><th>Assessment</th><th>Instrument/components</th><th>Cut-off points</th></tr>
<tr><td>Disease activity</td><td>ACR/EULAR remission criteria[45]
• SDAI
• CDAI
• Tender joint count (of 28)
• Swollen joint count (of 28)
• Patient global assessment (cm)
• CRP (mg/dL)</td><td>Remission:
• SDAI≤3.3
• CDAI≤2.8
• Tender joint count≤1
• Swollen joint count≤1
• Patient global assessment≤1
• CRP≤1</td></tr>
<tr><td>Disease activity, based on patient-reported outcomes</td><td>Patient Activity Scale-II (PAS-II)[21 28]
• HAQ-II (0−10)
• Pain (cm)
• Patient global assessment (cm)</td><td>• Remission: PAS-II≤0.25
• Low disease activity: 0.26<PAS-II≤3.7
• Moderate disease activity: 3.7<PAS-II<8.0
• High disease activity: PAS-II≥8.0</td></tr>
<tr><td>Disease activity, based on patient-reported outcomes</td><td>Routine Assessment of Patient Index Data 3 (RAPID3)[21 30]
• MDHAQ (0−10)
• Pain (cm)
• Patient global assessment (cm)</td><td>• Remission: RAPID3≤3
• Low disease activity: 4≤RAPID3≤6
• Moderate disease activity: 7≤RAPID3≤12
• High disease activity: RAPID3≥13</td></tr>
<tr><td>Change in status (primarily used in clinical trials; considered obsolete[9])</td><td>EULAR response criteria[33]
• DAS28 at endpoint
• Improvement (Δ) in DAS28 from baseline</td><td><table><tr><th>DAS28 at endpoint</th><th>ΔDAS28 ≤1.2</th><th>0.6<ΔDAS28≤1.2</th><th>ΔDAS28 ≤0.6</th></tr><tr><td>DAS28≤3.2</td><td>Good</td><td>Moderate</td><td>No</td></tr><tr><td>3.2<DAS28≤5.1</td><td>Moderate</td><td>Moderate</td><td>No</td></tr><tr><td>DAS28>5.1</td><td>Moderate</td><td>No</td><td>No</td></tr></table></td></tr>
<tr><td>Change in status (primarily used in clinical trials)</td><td>ACR response criteria[34 46 47]
• Tender joint count
• Swollen joint count
• Patient assessment of pain
• Patient assessment of physical function
• Patient global assessment
• Physician global assessment
• Acute phase reactant</td><td>ACR20, ACR50, ACR70 if improvements of at least 20%, 50%, 70% relative to baseline in:
• Tender joint count
• Swollen joint count
• At least three of the remaining criteria</td></tr>
<tr><td>Additional measures[14]</td><td></td><td></td></tr>
<tr><td>Fatigue</td><td>Various instruments, including VAS and questionnaires[48]</td><td>—</td></tr>
<tr><td>Radiological damage</td><td>Various scoring methods to assess joint damage[35]</td><td>—</td></tr>
</table>

Source: Scott *et al.*[14], Smolen *et al.*[12] and references in table.
Abbreviations: ACR, American College of Rheumatology; COS, Core Outcome Set; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire Disability Index (also known as HAQ, Health Assessment Questionnaire); MDHAQ, Multidimensional Health Assessment Questionnaire; MHAQ, Modified Health Assessment Questionnaire; RA, Rheumatoid Arthritis; VAS, Visual Analog Scale.
Note: The RA COS is a set of endpoints recommended to be assessed in clinical trials of RA.[24] ACR20/50/70 criteria are used only in clinical studies but not in clinical practice as they assess a change in status and do not have a continuous scale.[12 14]

3.2 Treatment of rheumatoid arthritis

The target of RA treatment is clinical remission or at least low disease activity (see Table 2), and treat-to-target strategies are recommended to achieve and maintain clearly defined treatment endpoints.[8 12 27 45 49] Overall, treatment of RA should prevent and stop damage to joints and preserve function.[12 50 51]

Several guidelines recommend treatment strategies, primarily based on pharmaceutical interventions, to achieve these treatment targets. Here, we focus on the treatment principles, recommendations, and pathways laid out by the 2019 EULAR Recommendations for management of RA with synthetic and biological DMARDs[8], the 2015 ACR Guideline for the treatment of RA[49] (please note that, at the time of writing in March/April 2020, the 2019 ACR Guideline was in the process of being updated and not yet publicly available[22]), and German guidelines for management of early RA[52] and for DMARD-based management of RA[9]. The Swiss Society for Rheumatology publishes drug-specific guidance ("Behandlungsempfehlung") on their website and otherwise refers to EULAR and ACR guidelines.[53]

3.2.1 Treatment principles

Guidelines lay out several general principles that should inform RA therapy. These include:

- Treatment of RA should provide best care. Decision-making should be shared between the patient and the treating rheumatologist.[8 9 49 52]
- Therapy decisions should be made according to prior therapy, disease activity, functional capacity, presence of erosions, safety, and comorbidity.[8 9] As therapy may need to be adapted, drugs with different modes of action should be accessible to patients.[8]
- Treatment decisions should factor in costs to patients, healthcare systems, and society.[8 9] The 2019 EULAR guideline explicitly mentions the potential of biosimilars, if priced low enough, to reduce high treatment costs and inequity in access to treatment.[8] Notably, the 2015 ACR guidelines adds the caveat that "arbitrary switching between RA therapies"[49] to meet specific payer or healthcare insurance policies is not recommended in patients with low disease activity or in clinical remission

3.2.2 Pharmaceutical treatment recommendations

Guidelines also lay out specific recommendations for pharmaceutical treatment. We summarise key recommendations here but note that treatment strategies are not a key focus of the HTA as the infliximab reference product and biosimilar take the same place in the treatment algorithm. It should be noted that guidelines may differ in classifying a specific suggestion as a treatment principle or a recommendation, and that there may be differences in guidelines as to which treatments are preferred at which step

- Symptoms such as pain and stiffness can be treated with analgesics or non-steroidal anti-inflammatory drugs.[14 52 54] These drugs do not modify the disease.
- DMARD therapy should be started as soon as RA is diagnosed.[8 9 25 52] Early treatment initiation has been shown to be associated with improved long-term outcomes. DMARD initiation within 1 year, relative to 1 to 5 years, of symptom onset was associated with reduced long-term rates of radiographic progression.[55 9 52]
- Patients should be treated to the target of sustained disease remission, e.g. as defined by ACR/EULAR criteria (Table 2).[8 9 49 52] If required, low disease activity instead of remission may be set as the treatment target.. If there is no improvement within 3 months of treatment start or if the target is not reached within 6 months of treatment start, therapy should be adapted.[8 9 52]
- The first treatment strategy should include the csDMARD methotrexate.[8 9 49 52] Initial therapy should also involve glucocorticoids to reduce symptoms and inflammation, but they should be tapered as quickly as possible to avoid long-term side effects.[8 9 52] Throughout the treatment course, glucocorticoids may be used to treat RA flares, particularly when changing DMARDs or as intra-articular injections for individual active joints.[8 14 49]
- If the treatment target is not achieved with the first csDMARD-based approach, therapy needs to be escalated. The 2015 ACR guidelines specify as feasible escalation options csDMARD combination, biologic therapy, or the targeted synthetic DMARD (tsDMARD) tofacitinib (a Janus kinase inhibitor), with no order of preference.[49] In contrast, the EULAR[8] and German[9] guidelines recommend to factor in patient prognosis: If the patient has no poor prognostic factors, therapy escalation should involve additional csDMARDs, likely in combination. If this strategy fails, bDMARDs or tsDMARDs should be used.[9] If the patient has poor prognostic factors, therapy escalation should involve adding a bDMARD or a tsDMARD to csDMARDs (ideally methotrexate).
- If further escalation is required, other bDMARDs or tsDMARDs should be considered, with 2015 ACR guidelines expressing a preference to choose a non-TNF inhibitor over tsDMARDs if a TNF inhibitor had been used before.[8 9 49]
- If the patient achieves sustained remission after tapering glucocorticoids, bDMARDs and tsDMARDs may be tapered, particularly when given with csDMARD.[8 9] No definition of “sustained” remission currently exists, but 6 months are frequently used.[8 25]

While pharmaceutical treatment of RA has advanced considerably in recent decades, open questions remain, e.g. on how drugs work and interact, when to initiate which therapy (e.g. in early RA), how to increase the share of patients achieving remission and how to perform treatment deescalation.[9 12]

3.2.3 Supportive treatment

Pharmaceutical treatment can be complemented with non-pharmaceutical treatment. Supportive treatment includes physiotherapy and occupational therapy as well as physical activity, foot care, psychological support, lifestyle adaptations and patient education.[14 52 56] Surgery of joints, especially joint replacement, may also be considered.[14]

3.3 Epidemiology and burden of rheumatoid arthritis

3.3.1 Epidemiology

The prevalence of RA is estimated at 0.5−1.0% in developed countries, with an estimated 85,000 prevalent patients in Switzerland and almost 20 million prevalent patients globally.[57–61] Estimates for incidence vary more widely but generally range between 25−50 new cases per 100,000 population per year, which translates to approximately 2,100−4,300 incident cases per year in Switzerland.[59 62] The risk of developing RA is increased twofold in women (lifetime risk approximately 3.6%) relative to men (lifetime risk approximately 1.7%).[59 63] Similarly, the risk of developing RA increases with age, with mean disease onset between 55-65 years.[57 59]

3.3.2 Burden of rheumatoid arthritis

Rheumatoid arthritis is, firstly, associated with a substantial mortality and morbidity burden. All-cause mortality in patients with RA is elevated by approximately 50% relative to the general population, with higher risk in patients with persistently high disease activity.[64 65] This increased mortality has been attributed not only to RA activity but also to elevated risks of comorbidities among patients with RA.[59 65–67] In particular, the risk of cardiovascular and respiratory disease is increased in patients with RA relative to the general population.[14 65 66 68] Treatment with TNF-alpha inhibitors such as infliximab is associated with reduced mortality relative to treatment csDMARDs.[64]Treatment itself may be associated with adverse events (AEs), such as infection at infusion/injection sites or tuberculosis (with some TNF inhibitors).[14 69]

Rheumatoid arthritis is, secondly, associated with a psychological burden on patients and reduced quality of life. In a meta-analysis based on a systematic review of observational studies reporting Short Form (SF)-36 results for adult patients with RA, the disease was found to have a considerable impact on quality of life.[70] Quality of life in more than 22,000 patients, with mean RA duration from less than 1 year to 17 years, was compared with the general population and with patients with other long-term diseases. Individuals with RA had lower quality of life than the general population in the United States (US) and

United Kingdom (UK) and than individuals with hypertension, type 2 diabetes, and myocardial infarction.[70]

Regarding disease acceptance, a qualitative study in patients with RA from the Italian-speaking region of Switzerland showed that acceptance was a complex process that required patients to find a way between grieve for lost capabilities and continued pursuit of one's own goals and values.[71] Acceptance was particularly difficult for patients who were diagnosed later (often too late, in many patient's opinion) in life as these patients experienced the disease as a more significant turning point in their lives.

Rheumatoid arthritis is, thirdly, an economic burden on healthcare systems and society (notably, the economic burden of arthritis in Switzerland was already pointed out in a 1948 paper on productivity losses due to arthritis[72]). Both direct medical costs (in particular drug costs) and productivity losses due to reduced work capabilities or absenteeism contribute to this economic burden.

Direct medical costs of RA in Switzerland were estimated at CHF 791 million in 2011, with per-patient costs of CHF 15,063.[73] A review of studies published since 2000 on costs of rheumatoid arthritis suggested that drug costs generally were the largest component in direct costs (up to 87% of direct costs, depending on the country).[74]

RA is also associated with considerable productivity losses, in particular due to disability-related productivity losses.[66 75] For Switzerland in 2011, productivity losses were estimated at CHF 1,534 billion (or CHF 29,210 per patient), i.e. almost double direct medical costs.[73] Overall, a recent review showed that productivity losses, measured with the human capital approach in most studies, accounted for 39% to 86% of total RA-related costs, depending on the country).[74]

4 Technology

The technology considered in this HTA is infliximab, given with concomitant methotrexate to patients with RA who failed standard therapy. More specifically, the focus is on using one version of infliximab, namely infliximab biosimilar, instead of another version, namely the infliximab reference product.

4.1 Technology description

Infliximab may be called a “biologic”, a “monoclonal antibody” or a “TNF-alpha inhibitor”, and reference may made to the “infliximab reference product” or an “infliximab biosimilar”. In this section, we provide an overview of what these terms mean and we describe infliximab, including its indications, dosage and administration.

4.1.1 Key terminology and context

Biologics are drugs produced by living systems, such as animal and plant cells or microorganisms.[76] Biologic drugs are large, complex, heterogeneous molecules relative to chemically synthesized small-molecule drugs, which makes them difficult to manufacture.[76 77] Importantly, as biologics are produced by living organisms, they change from batch to batch.[76–79] Changes in manufacturing process often lead to changes in the biologic, to the extent that “widely used biologicals are not, after several changes to their original manufacturing process, anymore identical to the original version at the time of marketing authorization”[80].

A biologic drug is referred to as the **originator product** if it was the first drug with a specific substance (such as infliximab) to come to market. Subsequent drugs with this specific substance can enter the market after patent expiry of the reference product and are referred to as **biosimilars** (while the originator drug then becomes the **reference** drug). Importantly, they should not be called (or confused with) generic drugs, which are subsequent-entry products for small molecules: While copies of small molecules can be exact, due to the unambiguous characterisation of small molecules, biosimilars cannot be exact copies, due to the large, heterogeneous structure of their molecules.[77 81] Similar to their reference products, there may be batch-to-batch variation in biosimilar production.[78] Like generic drugs, biosimilars are usually priced lower than their respective reference products.[82]

The broad definition of biologics provided above captures a wide range of drugs, from vaccines to insulins, and disease areas, from cancer to diabetes. Here, we focus on biologics particularly relevant for the treatment of autoimmune diseases such as inflammatory bowel disease (IBD), ulcerative colitis (UC), and RA. Among such biologics, **monoclonal antibodies** (mAbs) are an important class. Monoclonal

antibodies are immunoglobulin molecules produced by cells that are single clones of a hybridoma parent cell.[76 83] These antibodies each target a single epitope. Depending on the origin of the parent cell, mAbs can be distinguished further into murine, chimeric, humanized, and human mAbs.[83]

4.1.2 Description of infliximab

Using the terminology just introduced, infliximab is a chimeric mAb with inhibition of TNF-alpha as its mode of action, which makes it a **TNF-alpha inhibitor**. Specifically, this mAb stops the pro-inflammatory TNF-alpha cytokine from activating the cellular TNF receptor complex.[84] It does this by binding to TNF-alpha in soluble and membrane-bound form, which results in the formation of stable immune complexes. TNF-alpha is then no longer capable of binding to its receptor, and intracellular signalling is blocked that would otherwise result in inflammatory activity.[84 85] Different pathways by which infliximab affects clinical outcomes have been identified, including regulation of the cytokine network, cell recruitment and vascular endothelial growth factor (another cytokine), and angiogenesis as well as prevention of cartilage catabolism and erosion of bone.[85]

Infliximab is administered as an intravenous (IV) two-hour infusion.[86] For patients with RA, the initial dose is 3 mg per kg body weight, given in weeks 0 (initial week), 2 and 6 and then every 8 weeks.[10 86] Doses can be up-titrated if response is insufficient although the Swiss Society for Rheumatology recommends not to exceed 10 mg per kg body weight every four weeks.[10 87] Infliximab is given with concomitant methotrexate. Infliximab is contraindicated in patients with:[10 86]

- Tuberculosis or other severe (acute or chronic) infections, including sepsis, abscesses, or opportunistic infections
- Heart failure classified as New York Heart Association classes III or IV
- Known hypersensitivity to infliximab or murine proteins

Infliximab is generally a safe medication but may still be associated with AEs. Frequent AEs including opportunistic and infusion site infections, serum sickness (a hypersensitive reaction to non-human proteins), headache and dizziness, flush, nausea, diarrhoea, abdominal pain and dyspepsia, hepatotoxicity, rash, pruritus, urticaria, increased sweating, dry skin, fatigue, and chest pain.[53 86 88 89]

4.1.3 Infliximab in Switzerland

The infliximab reference product (Remicade®, MSD Merck Sharp & Dohme AG) was approved in Switzerland in 1999 and has been included in the SL since July 2000. Two infliximab biosimilars, Inflectra® (Pfizer PFE Switzerland GmbH) and Remsima® (iQone Healthcare Switzerland SA), which both contain

the same CT-P13 product[90], have been included in the SL since October 2016.[91] In RA, use of infliximab is limited (*limitatio*) to patients with active RA after failure of prior standard therapy with DMARDs.[91]

Infliximab is associated with substantial costs to the Swiss healthcare system. It is noteworthy that the Swiss Society for Rheumatology, in their therapy recommendations for TNF-alpha inhibitors, suggested a maximum dose of 10 mg per kg body weight and per every 4 weeks with an explicit reference to treatment costs.[53] In addition, infliximab (like other TNF-alpha inhibitor) therapy requires prior costing approval by the medical officer ("Vertrauensarzt/Vertrauensärztin") of the patient's healthcare insurer and must be prescribed only by rheumatologists or in rheumatology departments of university hospitals and polyclinics.[91]

Currently (April 2020), public list prices for 100 mg of infliximab are CHF 830.90 for the reference product and CHF 627.25 for the biosimilars.[91] In 2018, estimated total costs for infliximab were CHF 133 million, equivalent to 1.7% of estimated total drug costs in Switzerland, with an estimated 6,976 individuals receiving infliximab (notably not all for RA as infliximab is also indicated for other autoimmune diseases such as psoriasis (PSO), psoriatic arthritis (PsA) or UC).[92] The reference product accounted for an estimated 83.2% of all infliximab purchases.

4.2 Alternative technologies to infliximab

This scoping report is about comparing the infliximab reference product and the infliximab biosimilar (Section 5). However, there are alternatives to infliximab for the treatment of RA, which we present here for the sake of completeness.

4.2.1 TNF-alpha inhibitors alternative to infliximab

Infliximab was the first but is not the only TNF-alpha inhibitor. Other drugs in this class which are used in the treatment of RA are adalimumab, golimumab, certolizumab pegol, and etanercept (etanercept is not an mAb but a fusion protein). As a class, TNF-alpha inhibitors are considered to have "revolutionized"[84] the treatment of RA in the past decades (see Section 3.2).[14] The five TNF-alpha inhibitors are generally clinically efficacious and slow radiographic progression, with relatively little difference in efficacy between agents although head-to-head comparisons are sparse.[12 84]

4.2.2 Alternative biologic classes to TNF-alpha inhibitors

In addition to TNF-alpha inhibitors, several other classes of biologics indicated for RA treatment exist.[54] A detailed review of these is beyond the scope of this report, so we list them here only briefly:

- Anti-IL 6 inhibitors, including tocilizumab and sarilumab.[93 94]
- Abatacept, a fusion protein inhibiting T lymphocytes.[95]
- Janus kinase inhibitors, including tofacitinib, baricitinib and upadacitinib.[96] These are not biologics but small molecules.

5 PICO criteria

The pre-scoping report and the research questions (Section 2) informed the PICO criteria (Table 3 to Table 5), which in turn informed our searches for evidence. In line with FOPH specifications, we used the terms “infliximab reference products” and “infliximab biosimilars” in the PICOs.

We specified outcome domains (e.g. “clinical efficacy”) and outcomes as per the pre-scoping report. However, as this is a scoping report and therefore designed to explore and map evidence, additional outcomes within those domains identified during the scoping phase were also considered.

Table 3 PICO criteria: patients with RA who initiate infliximab treatment (PICO 1)

Population**:**	Patients with RA who did not respond adequately to standard therapy with DMARDs
Intervention**:**	Initiate treatment with infliximab reference product [boDMARD]
Comparator**:**	Initiate treatment with infliximab biosimilar [bsDMARD]
Outcome**:**	*Clinical efficacy*: Clinical response, e.g. ACR criteria, Disease Activity Score 28, Clinical Disease Activity Index, Simplified Disease Activity Index, rheumatoid arthritis core set of outcomes including tender/swollen joint count, *PK/PD*: Pharmacokinetics (AUC, C_{max}) and pharmacodynamic outcomes, including acute phase reactants *Patient-reported outcome measures*: Functional status; patient global assessment; physician global assessment (grouped here for consistency though not technically a patient-reported outcome); pain; health-related quality of life *Safety*: Serious and important adverse events *Immunogenicity*: Anti-drug antibodies and neutralising antibodies *Treatment adherence*: Discontinuation and its reasons (targeting the nocebo effect) *Costs and health economic outcomes*: Cost-effectiveness and budget impact (setting-specific)

Source: Based on pre-scoping report and kick-off meeting with FOPH..
Abbreviations: ACR, American College of Rheumatology; AUC, Area Under Curve; boDMARD, biologic originator DMARD; bsDMARD, biosimilar DMARD; C_{max}, peak drug concentration; DMARD, Disease-Modifying Antirheumatic Drug; FOPH, Federal Office of Public Health; PD, Pharmacodynamics; PK, Pharmacokinetics; RA, Rheumatoid Arthritis.

Table 4 PICO criteria: patients with RA treated with infliximab reference product (PICO 2)

Population**:**	Patients with RA who did not respond adequately to standard therapy with DMARDs and are currently treated with infliximab reference product
Intervention**:**	Continue treatment with infliximab reference product [boDMARD]
Comparator**:**	Switch to treatment with infliximab biosimilar [bsDMARD]
Outcome**:**	As in Table 3

Source and abbreviations: as in Table 3

Table 5 PICO criteria: patients with RA treated with infliximab biosimilar (PICO 3)

Population**:**	Patients with RA who did not respond adequately to standard therapy with DMARDs and are currently treated with infliximab biosimilar
Intervention**:**	Continue treatment with infliximab biosimilar [bsDMARD]
Comparator**:**	Switch to treatment with infliximab reference product [boDMARD]
Outcome**:**	As in Table 3

Source and abbreviations: as in Table 3

6 HTA key questions

6.1 Specific questions based on central research questions

The central research questions (Section 2) for each of the three different populations of interest (Section 5) focus on (clinical) efficacy, effectiveness, safety, and cost-effectiveness. The aim of an HTA would therefore be to answer, for patients initiating infliximab biosimilars or switching from the reference product to infliximab biosimilar (or vice versa), the following questions:

- What is the clinical *efficacy* of the infliximab reference product relative to infliximab biosimilar and of the switch from one to the other? Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity). Efficacy refers to the "performance of [infliximab] under ideal and controlled circumstances"[97]. Efficacy is usually assessed in randomized clinical trials (RCTs). For biosimilars, RCTs are mostly equivalence trials: Their aim is not to demonstrate superiority or inferiority of a biosimilar relative to the reference product but to demonstrate equivalence.[98–100] Equivalence means that differences between treatments are clinically irrelevant. In practice, equivalence is established if the difference in clinical response is within a pre-specified interval, −Δ to + Δ. Choice of equivalence margins is challenging, with guidance suggesting that the margin should reflect the largest clinically acceptable difference between treatments while also being smaller than the minimum difference between the reference product and placebo.[99]
- What is the *effectiveness* of the infliximab reference product relative to infliximab biosimilar and of the switch from one to the other? Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (external validity). Effectiveness is assessed using real-world evidence (RWE), which include, for example, observational studies, pragmatic clinical trials, and post-marketing studies.[97 101]
- What is the *safety* of the infliximab reference product relative to infliximab biosimilar and of the switch from one to the other? Safety is a judgement of the harmful effects and their severity using the health technology. Relevant AEs are those that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (serious AEs) and those that occur repetitively and the most frequent (highest rate).[102] Safety can be assessed in RCTs and in RWE studies. The latter may provide a long-term perspective on safety and use comparatively larger sample sizes that help identify rare but serious AEs.

- What is the *health economic* perspective on the infliximab reference product relative to infliximab biosimilar in Switzerland and of the switch from one to the other? Health economic considerations include cost-effectiveness analysis (CEA), i.e. the assessment of at least two treatments with regard to their effectiveness in relation to their cost.[103] While CEA provides evidence to decision-makers on efficient resource allocation, it does not comment on affordability of a treatment – to assess affordability, budget impact analysis (BIA) is required. In addition to cost-effectiveness and budget impact analyses, more descriptive analyses of costs and resource use can be useful for decision-making. Notably, such analyses are not all likely to be transferable to the Swiss setting due to, among others, differences in healthcare systems and prescription practices. However, they would still provide valuable information on study designs and methods that could be used for similar assessments in the Swiss setting.

Beyond efficacy, effectiveness, safety and health economics, HTAs focus on additional domains of a technology:[104–107]

- What, if any, *ethical* issues are there regarding the reference product and biosimilar, in particular switch to biosimilar? Ethical issues include, among others, effects on healthcare distribution, patient autonomy as well as potential harm to patients.[108 109]
- What, if any, *legal* issues in Switzerland are there regarding the reference product and biosimilar, in particular switch to biosimilar? Legal issues include, among others, legal regulation of interchanging medications and therapeutic freedom.[107 110]
- What, if any, *social* and *sociocultural* issues are there regarding the reference product and biosimilar, in particular switch to biosimilar? These issues include, among others, effects of treatment on values and resource allocation within a society.[104]
- What, if any, *organizational* issues are there regarding the reference product and biosimilar, in particular switch to biosimilar? Organizational issues include, among others, policies for changing to biosimilars on a large scale.[111–113]

6.2 Additional outcomes of interests and additional questions

In agreement with the FOPH, we included additional outcomes that were considered relevant for (infliximab) biosimilars in the scoping report and would suggest their inclusion in an HTA.

6.2.1 *Additional outcomes for infliximab biosimilars*

- What is the *pharmacokinetic* (PK), *pharmacodynamic* (PD), and *immunogenicity* profile of the infliximab reference product relative to infliximab biosimilar, in particular in the context of switching? The comparability of reference products and biosimilars relies on comparative PK/PD assessments and biosimilar immunogenicity is frequently cited as a concern so we considered PK, PD, and immunogenicity results as important.[80 114 115]
- How do *PROM*s differ between the infliximab reference product and infliximab biosimilar, in particular in the context of switching? PROMs include RA-specific outcomes such as reported functional status and patient global assessment (we also group physician global assessment here) but also more general outcome measures such as HRQoL. We note that patient and physician global assessment also have clinical value in RA and indeed form part of many clinical outcome instruments (see Table 2).[38 40] Still, we group both assessments as PROMs as they are somewhat more subjective than assessment of joints and laboratory markers. In addition, separating patient assessment and other subjective instruments from more objective ones is helpful to identify nocebo effects (see next bullet point).[116 117]
- How do *treatment discontinuation* and its medical and non-medical reasons differ between the infliximab reference product and infliximab biosimilar, in particular in the context of switching? In the literature, there is some discussion around discontinuation of infliximab biosimilar, which was frequently reported to be due not to objective but to subjective worsening of disease, indicating a possible nocebo effect.[116 117] We therefore considered treatment discontinuation (or retention) rates in RCTs and RWE studies to be a relevant outcome, not least with regard to potential health economic modelling of infliximab biosimilars.

6.2.2 *Additional question on international regulation and reimbursement of biosimilars*

At the request of the FOPH, we included evidence on regulatory procedures for biosimilars in select countries (see Section 7). For a subset of countries, we also assessed evidence on pricing and reimbursement practices, in addition to those of Switzerland. We grouped evidence on regulatory and reimbursement policies within the legal domain.

7 Methodology of the literature search

We conducted two literature searches to inform this scoping report, one for evidence on efficacy, safety, effectiveness, and health economic outcomes (Section 7.1), the other for evidence on ethical, legal, social, and organizational (ELSO) outcomes (Section 7.2). We chose this approach as evidence on the former would need to be specific to infliximab and RA, whereas evidence on the latter was broader and included biosimilars in general (not just infliximab biosimilar or in the treatment of RA). This approach allowed us to develop tailored search strategies for each group of domains.

7.1 Literature search for efficacy, safety, effectiveness and health economic outcomes

7.1.1 Search strategies and data sources

We developed search strategies based on the PICO criteria (Section 5) in collaboration with a medical librarian (see Appendix 12.1-12.4). Our focus was on the PIC components, and we did not specify outcomes to avoid undue narrowing of search results.

The search strategies were implemented by the medical librarian in Cochrane Library, Medline (via EBSCOhost), Embase, EconLit (via EBSCOhost), and PsycInfo (via EBSCOhost) (Section 12).

Furthermore, we conducted a search in Google Scholar as *allintitle: infliximab biosimilar arthritis (all these words)*. This straightforward search reflected the search functionality available in the tool.

In addition, we searched websites of key HTA agencies (selection agreed in collaboration with the FOPH, see Section 12.3). Websites were searched, using built-in website functionality, for the keywords *infliximab* and *biosimilar* (and the respective translation in the local language):

For health economic results, we additionally searched the following registries/databases, using built-in website functionality for the keywords *infliximab* and *biosimilar.*

- CEA Registry, hosted at Tufts Medical Center (https://cevr.tuftsmedicalcenter.org/databases/cea-registry)
- National Health Service Economic Evaluation Database, hosted at the University of York's Centre for Reviews and Dissemination (https://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp)

Reference lists of studies included after full-text screening (see Section 7.1.3) were searched for additional relevant studies that had not previously been included.

7.1.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria were defined according to PICO criteria (Section 5) and were kept broad, with no restriction by publication period or study quality. We included studies with adult populations, in line with the age of RA onset (though we note that paediatric patients might receive infliximab for indications such as Morbus Crohn). Studies with a published full text in English, French, German, or Italian were eligible. In line with the "scoping" nature of this report, we did not specify concrete outcomes as inclusion or exclusion criteria as long as outcomes were within the domains outlined in Section 6.

Inclusion/exclusion criteria for studies on efficacy, effectiveness, safety, PK/PD, PROMs, and health economic outcomes are listed in Table 6. Studies had to be RCTs, RWE studies, or health economic analyses to be eligible for inclusion.

RWE studies and health economic analyses were included if they had been conducted in one of the target countries (defined in agreement with the FOPH, see below). The decisions to define target countries and which countries to include as target countries were made to obtain information from a broad range of settings relevant for Switzerland while keeping literature searches manageable for the scoping report.

Target countries included:

- Switzerland as the primary country of interest for the scoping report and HTA
- Austria, Belgium, Denmark, Finland, France, Germany, Great Britain, Netherlands, and Sweden and the UK as the reference countries used in the "Auslandpreisvergleich" (comparison of foreign prices) to assess cost-effectiveness of drugs in Switzerland
- The remaining Benelux country (Luxemburg) and the remaining Nordic country (Norway) not already included in the reference countries (see previous bullet points)
- Italy and Spain as important pharmaceutical markets in Europe
- Australia, Canada, and the United States, which are highly developed countries with important pharmaceutical markets

Table 6 Inclusion criteria for studies on efficacy, effectiveness, safety, PK/PD and PROMs

Criterion	Inclusion	Exclusion
Publication period	No restrictions	—
Publication status	Published full text available	Published full text not available (including conference abstracts)
Language	English, French, German or Italian	Not English, French, German or Italian
Setting	• RCT: all • RWE study and health economic analyses: Austria, France, Germany, Italy, Spain, the United Kingdom, Switzerland, Belgium, Luxemburg, Netherlands, Denmark, Finland, Norway, Sweden, Australia, Canada, United States	• Randomized controlled trials: none • Real-world evidence studies and health economic analyses: not in one of countries listed on the left
Study design/type	• RCT • RWE study, including observational and register-based studies • Health economic analysis, including costing studies, budget impact analyses, cost-minimization analyses, and full health economic evaluations	Not RCT, RWE study or health economic analysis
Study quality	No restrictions	—
Study population	Adult (≥18 years) patients with rheumatoid arthritis who failed standard therapy with disease-modifying antirheumatic drugs and • Initiate treatment with an infliximab product • Are currently treated with infliximab reference product • Are currently treated with infliximab biosimilar	• Animal studies • Patients with rheumatoid arthritis who have not failed standard therapy • Patients with rheumatoid arthritis treated with biological drugs other than infliximab • Patients without rheumatoid arthritis
Study intervention	• Initiate treatment with infliximab reference product + methotrexate • Continue treatment with infliximab reference product + methotrexate • Continue treatment with infliximab biosimilar + methotrexate	Any other intervention
Study comparator	• Initiate treatment with biosimilar + methotrexate • Switch to infliximab biosimilar + methotrexate • Switch to infliximab reference product + methotrexate	Any other comparator
Study outcomes	No restrictions	—

Abbreviation: PD, Pharmacodynamics; PICO, Population, Intervention, Comparator, Outcome; PK, Pharmacokinetics; PROM, Patient-Reported Outcome Measure; RCT, Randomized Clinical Trial; RWE, Real-World Evidence.

7.1.3 Study selection

Study results from searches in literature databases, Google Scholar, and websites were combined, and duplicates were removed. Titles and abstracts of studies were then screened, by two researchers independently, for meeting the inclusion criteria. For studies retained after title-abstract screening, full texts were reviewed independently by two researchers. From studies meeting inclusion criteria, study data relevant for the scoping report were extracted into a custom MS Excel workbook, again independently by two researchers (follow-up periods were converted to weeks, assuming an average of 365.25 days per year). Screening was conducted using the systematic review software CADIMA.[118]

As per the study protocol, we dual-screened hits for this search at all stages of the screening process and conflicts were resolved through consultation with a third reviewer. We developed an internal guidance document to assist members of staff with screening. After the first draft of this internal guidance was completed, two researchers screened titles and abstracts of a random sample of 100 hits to ascertain if criteria were clear and used consistently. We achieved a Kappa value of 82.7%, just above our pre-specified threshold of 80%. Still, we used our experiences from this initial screening to refine further the internal guidance before rolling it out among the project team.

All hits were assessed for all criteria, with two exceptions: When a hit was of the wrong study design and/or of a non-eligible publication status (a conference abstract or poster), we excluded this hit and did not assess the remainder of the criteria further in the interest of time and efficient resource use. During the initial title-abstract-screening of a random sample of hits, we noted that titles and abstracts rarely provided information on concomitant methotrexate treatment or prior failure of DMARD therapy. At the title-abstract-screening stage, we consequently excluded hits based on these criteria only if there was evidence that these criteria were definitely not met. A detailed assessment of these criteria was conducted during full-text screening.

7.2 Literature search for ethical, social, legal and organizational issues

7.2.1 Search strategies and data sources

We developed search strategies for ELSO outcomes in collaboration with a medical librarian (see Appendix 12.2). This search was not restricted by substance or patient population as we considered ethical, legal, and social aspects of biosimilars to apply broadly, regardless of specific substances or patient populations.

The search was implemented in Medline (via EBSCOhost) (Section 12.2). Furthermore, we conducted a search in Google Scholar as *allintitle: biosimilar (all these words) social legal law ethical ethics organizational (any of these words)*. This search reflected the search functionality available in the tool.

In addition, we searched websites of regulatory agencies using built-in website functionality for the keyword *biosimilar*. The list of agencies was drafted in agreement with the FOPH (see Section 12.4).

7.2.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria were developed in accordance with those of the efficacy, safety, effectiveness, and health economic search (see Table 6). For studies of organizational outcomes, we restricted eligibility to the same countries for which RWE studies and health economic analyses were eligible (Table 7). However, we imposed no study design restrictions as we expected discussions of ELSO outcomes to be presented in a variety of study designs.

Table 7 Inclusion criteria for studies on ELSO outcomes

Criterion	Inclusion	Exclusion
Publication period	As for Table 6	
Publication status		
Language		
Setting	For ethical, legal, social aspects: all settings For organizational aspects: as for real-world evidence in Table 6	For ethical, legal, social aspects: none For organizational aspects: as for real-world evidence in Table 6
Study design/type	No restrictions	—
Study quality	As for Table 6	
Study population	No restrictions	—
Study intervention and comparator	Discussion of biosimilars (any, not just of infliximab)	No discussion of biosimilars
Study outcomes	Discussion of ethical, legal, social, or organizational aspects, including policies, insurance and reimbursement models, and regulatory approaches	No discussion of ethical, legal, social, or organizational aspects, including policies, insurance and reimbursement models, and regulatory approaches

Abbreviation: ELSO, Ethical, Legal, Social, Organizational.

7.2.3 Study selection

The search for ELSO issues was conducted as a targeted search. A single researcher screened and reviewed the literature and identified studies relevant to the ELSO domains in CADIMA.[118]

Note that this review was not systematic. We considered this to be an appropriate approach as the primary purpose was to identify key aspects relevant to ELSO outcomes but not to provide an exhaustive or systematic review of the literature on these domains. In particular for regulatory issues, selecting

current guidance documents and recent studies was deemed preferable over summarizing all studies, some of which were (partly) obsolete due to changes in the often fairly dynamic regulation of biosimilars.

7.3 Quality of evidence assessment

Evidence quality was not assessed formally at the scoping stage but will be at the HTA stage.

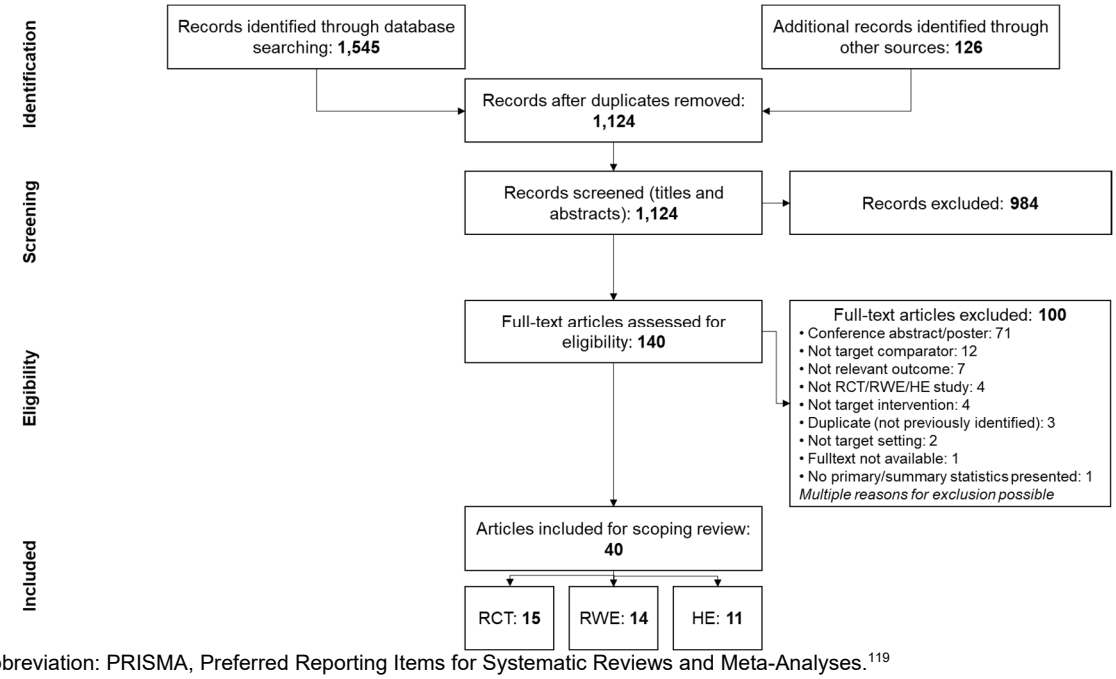
8 Synthesis of evidence base

8.1 Evidence base pertaining to efficacy, effectiveness, safety and cost-effectiveness

8.1.1 PRISMA flow diagram

The search for evidence pertaining to efficacy, safety, effectiveness and health economic outcomes yielded 1,545 hits from literature databases and an additional 126 hits from other sources (Figure 2).

Figure 2 PRISMA flow diagram for efficacy, safety, effectiveness, health economic search



Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[119]

Of the 1,124 unique hits, 984 were excluded during title-abstract-screening. Of the remaining 140 articles whose full texts were screened, 100 were excluded, most frequently because they were conference abstracts/posters or because they did not include information on infliximab biosimilars (see Section 12.5.1). Forty articles were retained for the scoping report, including 15 studies reporting on RCTs, 14 RWE studies and 11 health economic analyses

8.1.2 Efficacy and safety as well as PK/PD, PROMs, immunogenicity and treatment discontinuation outcomes in clinical settings

8.1.2.1 Evidence table for RCTs

Fifteen studies reporting on seven RCTs, including their extensions, were identified (Table 8).[4–7 98 120–129] By publication date, the first study was from 2013[4] and the most recent study from 2020[127].

CoI (Conflict of Interest) and funding: All studies included in the scoping report had at least one author with a CoI. All studies were funded at least in part by the pharmaceutical industry, with the exception of the NOR-SWITCH trial, which was funded by the Norwegian government.[7 128]

Countries, settings: Most RCTs were multinational, with the exception of NOR-SWITCH (conducted in Norway) and two RCTs from Japan[124 126 129]. Most studies had a parallel-group design, with the exception of three single-arm extension studies[6 128 129].

Indications: As per our inclusion criteria, all RCTs included (only) patients with RA. The NOR-SWITCH trial also included patients with Morbus Crohn, PsA, psoriasis, SpA and UC, and the trial was not powered to detect differences in outcomes between indications.[7 128]

Switch, arms and open-label components: Almost all RCTs investigated a switch to infliximab biosimilar at some point.[6 7 98 120 124 127–129] Upon switch, most studies continued open-label.[6 124 127–129] An exception was the LIRA trial, which neither assessed switch nor included an open-label component.[123]

With regard to comparisons and study arms, initial trial phases always compared infliximab reference product and biosimilar. Different transition designs were chosen for implementing and assessing switch.[130 131] In the REFLECTIONS B537-02 trial, half of the patients receiving the reference product were switched to biosimilar after 30 weeks, while the other half and patients initially receiving biosimilar continued on their respective initial medication. After 54 weeks, patients still treated with the reference product were also switched to biosimilar.[120 127] A similar design was chosen by Smolen *et al.*[98] In PLANETRA, NOR-SWITCH, and the study by Tanaka *et al.*, all patients initially receiving the reference product switched to biosimilar so studies continued as single-arm extension studies.[6 128 129]

Follow-up, sample size, age, and sex: Follow-up periods ranged from 30 weeks up to 105 weeks in extension studies. Commonly used assessment time steps were 30, 54, and 78 weeks. Sample sizes ranged from 71 participants[124] to 650 participants[4 122]. All RCTs recruited both women and men. Participants' minimum age was between 18 and 20 years in all trials. All trials that specified a maximum age for inclusion used 75 years.

Infliximab dose and schedule, prior medication: By design, infliximab was dosed at 3 mg per kg body weight, at weeks 0 (initiation), 2, 6, and then every 8 weeks in all trials except for NOR-SWITCH, in which doses and schedules were continued from participants' prior doses and schedules. For all trials, only participants with at least 4 weeks of prior stable methotrexate dose, between 6 and 25 mg per week, were eligible.

Primary endpoints: Most RCTs specified clinical efficacy outcomes, particularly ACR20 or DAS28, as their primary endpoints. Exceptions were the Japanese trial by Takeuchi *et al.*[126], which specified a PK endpoint (C_{max}) as its primary endpoint, and its extension by Tanaka *et al.*[129], which specified a safety

endpoint (AEs) as its primary endpoint. The single-arm extension of PLANETRA did not explicitly specify a primary endpoint.[6]

Table 8 Characteristics of included RCTs

First author, year	Study name, ID	CoI for at least one author	Industry funding	Countries	Indications	RCT design	Switch assessed	Arms	Follow-up (weeks)	Total sample size	Age (years) eligible	Infliximab dose (mg per kg)	Infliximab administration	Primary endpoint
Takeuchi *et al.*, 2015[126]	JapicCTI-111620	Yes	Yes	Japan	RA	PG	No	Reference product vs biosimilar	54	101	20 to 75	3	0-2-6-every 8w	PK/PD (C max)
Tanaka *et al.*, 2017[129]	JapicCTI-142419	Yes	Yes	Japan	RA	Single-arm extension	Yes	Switched to biosimilar vs continued on biosimilar	105	71	20 to 75	3	0-2-6-every 8w	Safety (AE)
Lila *et al.*, 2019[123]	LIRA, NCT02762838	Yes	Yes	Multinational	RA	PG	No	Reference product vs biosimilar	54	418	18 to 75	3	0-2-6-every 8w	Clinical efficacy (ACR20)
Matsuno *et al.*, 2019[124]	NCT01927263	Yes	Yes	Japan	RA	PG (biosimilar for all after 30w)	Yes	Reference product vs biosimilar	54	242	20 to 75	3	0-2-6-every 8w	Clinical efficacy (DAS28-ESR)
Choe *et al.*, 2017[121]	NCT01936181, EudraCT 2012-005733-37	Yes	Yes	Multinational	RA	PG	No	Reference product vs biosimilar	30	584	18 to 75	3	0-2-6-every 8w	Clinical efficacy (ACR20)
Smolen *et al.*, 2017[125]	NCT01936181, EudraCT 2012-005733-37	Yes	Yes	Multinational	RA	PG	No	Reference product vs biosimilar	54	505	18 to 75	3	0-2-6-every 8w	Clinical efficacy (ACR20)
Smolen *et al.*, 2018[98]	NCT01936181, EudraCT 2012-005733-37	Yes	Yes	Multinational	RA	PG	Yes	Continued reference product vs switch to biosimilar vs continued biosimilar	78	396	18 to 75	3	0-2-6-every 8w	Clinical efficacy (ACR20)
Jørgensen *et al.*, 2017[7]	NOR-SWITCH, NCT02148640	Yes	No	Norway	Crohn, PsA, Pso, RA, SpA, UC	PG	Yes	Reference product vs biosimilar	52	482	>=18	Unchanged from baseline	unchanged from baseline	Clinical efficacy (DAS28-ESR)
Goll *et al.*, 2019[128]	NOR-SWITCH, NCT02148640, EudraCT 2014-002056-40	Yes	No	Norway	Crohn, PsA, Pso, RA, SpA, UC	PG	Yes	Switched to biosimilar vs continued biosimilar	78	380	>=18	Unchanged from baseline	unchanged from baseline	Clinical efficacy (DAS28-ESR)
Yoo *et al.*, 2013[4]	PLANETRA, NCT01217086	Yes	Yes	Multinational	RA	PG	No	Reference product vs biosimilar	30	606	18 to 75	3	0-2-6-every 8w	Clinical efficacy (ACR20)

First author, year	Study name, ID	CoI for at least one author	Industry funding	Countries	Indications	RCT design	Switch assessed	Arms	Follow-up (weeks)	Total sample size	Age (years) eligible	Infliximab dose (mg per kg)	Infliximab administration	Primary endpoint
Yoo *et al.*, 2016[5]	PLANETRA, NCT01217086	Yes	Yes	Multinational	RA	PG	No	Reference product vs biosimilar	54	455	18 to 75	3	0-2-6-every 8w	Clinical efficacy (ACR20)
Yoo *et al.*, 2017[6]	PLANETRA, NCT01571219	Yes	Yes	Multinational	RA	Single-arm extension	Yes	Switched to biosimilar vs continued biosimilar	102	302	18 to 75	3	every 8w	No info (Not applicable)
Alten *et al.*, 2019[120]	REFLECTIONS B537-02, NCT02222493	Yes	Yes	Multinational	RA	PG	Yes	Continued reference product vs switch to biosimilar vs continued biosimilar	54	566	>=18	3	every 8w	Clinical efficacy (ACR20)
Cohen *et al.*, 2018[122]	REFLECTIONS B537-02, NCT02222493, EudraCT 2013-004148-49	Yes	Yes	Multinational	RA	PG	No	Reference product vs biosimilar	30	650	>=18	3	0-2-6-every 8w	Clinical efficacy (ACR20)
Cohen *et al.*, 2020[127]	REFLECTIONS B537-02, NCT02222493, EudraCT 2013-004148-49	Yes	Yes	Multinational	RA	PG	Yes	Switched to biosimilar after 30w vs switched to biosimilar after 54w vs continued biosimilar	78	505	>=18	3	every 8w	Clinical efficacy (ACR20)

Abbreviations: ACR, American College of Rheumatology; AE, Adverse Event; CoI, Conflict of Interest; Crohn, Morbus Crohn; ESR, Erythrocyte Sedimentation Rate; PD, Pharmacodynamic; PG, Parallel-Group; PK, Pharmacokinetic; PsA, Psoriatic Arthritis; Pso, Psoriasis; RA, Rheumatoid Arthritis; RCT, Randomized Controlled Trial; UC, Ulcerative Colitis; w, Weeks;

8.1.2.2 Findings on efficacy, safety, PK/PD, PROMs, and immunogenicity outcomes from RCTs

Outcomes in all domains were reported by identified studies, with a clear focus on outcomes related to clinical efficacy and safety (Figure 3).

Clinical efficacy: This was the domain for which the most data were available, in particular for ACR criteria and DAS28 (both calculated with ESR and with CRP). Other indices and EULAR response were also assessed frequently. Joint counts and radiologic damage were reported less frequently (Table 9).

Immunogenicity: All studies reported on anti-drug antibodies (ADAb) and ten also reported on neutralising antibodies.

PK/PD: Several studies reported PK/PD outcomes, in particular minimum and maximum serum concentrations and acute phase reactants. Other measures were reported less frequently, with most reported only by a single study.[4]

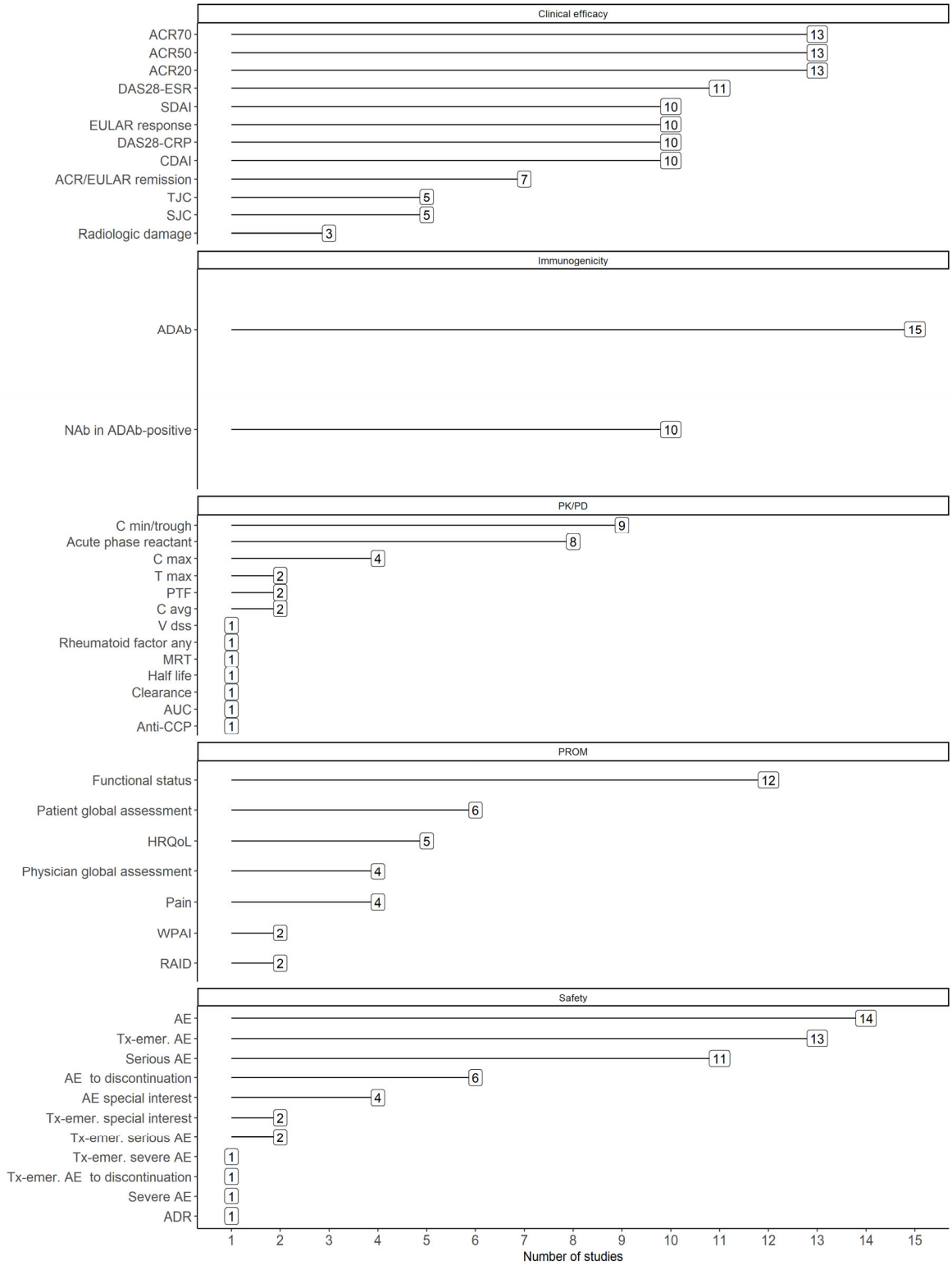
PROMs: Nearly all studies reported on PROMs, in particular on functional status, which was the most widely used instrument. Patient and physician global assessment were also reported (as separate outcome measures, i.e. not part of composite disease indices), as was HRQoL. Pain was reported as a separate outcome in four studies. The remainder of PROMs was reported in at most two studies.

Safety: All studies reported on safety. Frequent outcome measures included AEs, treatment-emergent AEs, and serious AEs. Terminology varied between studies, with some also reporting on serious (and severe) treatment-emergent AEs and AEs leading to discontinuation of treatment.

Assessment of RCT-based evidence: RCTs included in the scoping review aimed to assess the use of infliximab biosimilars compared to infliximab reference product, as well as the possible outcomes resulting from a switch of the reference product to an infliximab biosimilar. Studies were similar in that they were (mostly) multinational studies and included adults of both sexes (although one must be careful in assuming that the population distribution is similar), but sample sizes varied considerably.

Efficacy and safety outcomes were reported frequently, and most studies reported results for all relevant outcome domains. Information was also available for PROM and PK/PD outcomes. Notably, study results, as per authors' conclusions, were consistent across studies and indicated that infliximab reference product and infliximab biosimilars were similar in both infliximab-naïve patients and switching patients with regard to efficacy, safety, PK/PD, immunogenicity, and PROM (Table 9).

Figure 3 Outcomes from RCTs



Source: Own calculations.
Abbreviations: ACR, American College of Rheumatology; ADAb, Anti-Drug Antibody; ADR, Adverse Drug Reaction; AE, Adverse Event; anti-CCP, Anticyclic Citrullinated Peptide; AUC, Area Under Curve; $C_{avg/max/min\ or\ trough}$, average/maximum/minimum serum concentration; CDAI; Clinical Disease Activity Index; CRP, C-Reactive Protein; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; EULAR, European League Against Rheumatism; HRQoL, Health-Related Quality of Life; PD, Pharmacodynamics; PK, Pharmacokinetics; PROM, Patient-Reported Outcome Measures; PTF, Peak-to-Trough Fluctuation Ratio; RAID, Rheumatoid Arthritis Impact of Disease; RCT, Randomized Controlled Trial; SDAI, Simplified Disease Activity Index; SJC, Swollen Joint Count; TJC, Tender Joint Count; T max, time to maximum serum concentration; Tx, Treatment; V_{dss}, Volume of Distribution Steady-State Method; WPAI, Work Productivity and Activity Impairment Questionnaire.

Table 9 Outcomes by RCT

First author, year	Study name	Switch	Clinical efficacy	Immunogenicity	PK/PD	PROM	Safety	Authors' conclusion (in abstract/summary)
Cohen *et al.*, 2020[127]	REFLECTIONS B537-02	Yes	ACR/EULAR remission, ACR20, ACR50, ACR70, DAS28-CRP, EULAR response, SJC, TJC	ADAb, NAb in ADAb-positive	C min/trough	Functional status	AE, AE special interest, AE to discontinuation, Serious AE, Tx-emer. AE	Results to week 78 continue to support the efficacy, safety, and immunogenicity of PF-SZ-IFX [biosimilar] in patients with moderate-to-severe active RA. There were no clinically meaningful differences between groups, independent of a single treatment transition from IFX-EU [reference product] to PF-SZ-IFX at week 30 or week 54. (p. 1)
Alten *et al.*, 2019[120]	REFLECTIONS B537-02	Yes	ACR/EULAR remission, ACR20, ACR50, ACR70, DAS28-CRP, EULAR response, SJC, TJC	ADAb, NAb in ADAb-positive	Acute phase reactant	Functional status	AE, AE special interest, Tx-emer. AE	The similar efficacy, safety and immunogenicity of PF-SZ-IFX [biosimilar] compared with ref-IFX [reference product] were maintained for up to 54 weeks and were not affected by blinded treatment switch from ref-IFX to PF-SZ-IFX at week 30. (p. 1)
Cohen *et al.*, 2018[122]	REFLECTIONS B537-02	No	ACR/EULAR remission, ACR20, ACR50, ACR70, DAS28-CRP, EULAR response	ADAb, NAb in ADAb-positive	Acute phase reactant, C max, C min/trough	Functional status	AE, AE special interest, Tx-emer. AE	PF-06438179/GP1111 [biosimilar] and infliximab-EU [reference product] demonstrated similar efficacy, safety, immunogenicity, and PK with or without dose escalation in patients with moderate to severe active RA on background methotrexate. (p. 1)
Yoo *et al.*, 2017[6]	PLANETRA	Yes	ACR20, ACR50, ACR70, DAS28-CRP, DAS28-ESR, EULAR response, SJC, TJC	ADAb, NAb in ADAb-positive	Acute phase reactant	Physician global assessment, Functional status, Pain, Patient global assessment	Tx-emer. AE to discontinuation, Tx-emer. serious AE, Serious AE, Tx-emer. special interest, Tx-emer. AE	Comparable efficacy and tolerability were observed in patients who switched from RP [reference product] to its biosimilar CT-P13 for an additional year and in those who had long-term CT-P13 treatment for 2 years. (p. 355)
Yoo *et al.*, 2016[5]	PLANETRA	No	ACR20, ACR50, ACR70, CDAI, DAS28-CRP, DAS28-ESR, EULAR response, Radiologic damage, SDAI	ADAb, NAb in ADAb-positive	Acute phase reactant, C max, C min/trough	Functional status, HRQoL, Pain, Patient global assessment	AE, Tx-emer. AE	CT-P13 [biosimilar] and RP [reference product] were comparable in terms of efficacy (including radiographic progression), immunogenicity and PK/PD up to week 54. The safety profile of CT-P13 was also similar to that of RP. (p. 1)
Yoo *et al.*, 2013[4]	PLANETRA	No	ACR/EULAR remission, ACR20, ACR50, ACR70, CDAI, DAS28-ESR, DAS28-CRP, EULAR response, SDAI, SJC, TJC	ADAb	Acute phase reactant, Anti-CCP, Rheumatoid factor any, C avg, C max, C min/trough, PTF, T max	Physician global assessment, Pain, Functional status, HRQoL, Patient global assessment	AE, Serious AE, Tx-emer. AE	CT-P13 [biosimilar] demonstrated equivalent efficacy to INX [reference product] at week 30, with a comparable PK profile and immunogenicity. CT-P13 was well tolerated, with a safety profile comparable with that of INX. (p. 1613)

First author, year	Study name	Switch	Clinical efficacy	Immunogenicity	PK/PD	PROM	Safety	Authors' conclusion (in abstract/summary)
Goll *et al.*, 2019[128]	NOR-SWITCH	Yes	ACR/EULAR remission, CDAI, DAS28-ESR, SDAI	ADAb	Acute phase reactant, C min/trough	Physician global assessment, Functional status, HRQoL, Patient global assessment, RAID, WPAI	AE, Serious AE, AE to discontinuation, Tx-emer. AE	The NOR-SWITCH extension showed no difference in safety and efficacy between patients who maintained CT-P13 [biosimilar] and patients who switched from originator infliximab to CT-P13, supporting that switching from originator infliximab to CT-P13 is safe and efficacious. (p. 654)
Jørgensen *et al.*, 2017[7]	NOR-SWITCH	Yes	ACR/EULAR remission, CDAI, DAS28-ESR, SDAI	ADAb	Acute phase reactant, C min/trough	Physician global assessment, Functional status, HRQoL, Patient global assessment, RAID, WPAI	AE to discontinuation, AE, Serious AE, Tx-emer. AE	The NOR-SWITCH trial showed that switching from infliximab originator to CT-P13 [biosimilar] was not inferior to continued treatment with infliximab originator according to a prespecified non-inferiority margin of 15%. The study was not powered to show non-inferiority in individual diseases. (p. 2304)
Matsuno *et al.*, 2019[124]	No info	Yes	ACR20, ACR50, ACR70, DAS28-CRP, DAS28-ESR	ADAb, NAb in ADAb-positive	C min/trough	Not reported	AE, AE to discontinuation, Tx-emer. AE	BS [biosimilar] demonstrated equivalent efficacy and safety to RP [reference product] at treatment weeks 14 and 30, and long-term safety until week 54 in Japanese RA patients. (p. 1537)
Smolen *et al.*, 2018[98]	No info	Yes	ACR20, ACR50, ACR70, CDAI, DAS28-ESR, EULAR response, SDAI	ADAb, NAb in ADAb-positive	Not reported	Not reported	AE, AE special interest, Serious AE, Tx-emer. serious AE, Tx-emer. AE	The efficacy, safety and immunogenicity profiles remained comparable among the INF/SB2 [reference product, then switched to biosimilar], INF/INF [continued reference product] and SB2/SB2 [continued biosimilar] groups up to week 78, with no treatment-emergent issues or clinically relevant immunogenicity after switching from INF to SB2. (p. 234)
Choe *et al.*, 2017[121]	No info	No	ACR20, ACR50, ACR70, CDAI, DAS28-ESR, EULAR response, SDAI, SJC, TJC	ADAb, NAb in ADAb-positive	Acute phase reactant, C min/trough	Functional status, Pain, Patient global assessment	AE, Serious AE, Tx-emer. AE	SB2 [biosimilar] was equivalent to INF [reference product] in terms of ACR20 response at week 30. SB2 was well tolerated with a comparable safety profile, immunogenicity and PK to INF. (p. 58)
Tanaka *et al.*, 2017[129]	No info	Yes	ACR20, ACR50, ACR70, CDAI, DAS28-CRP, DAS28-ESR, EULAR response, SDAI	ADAb	Not reported	Functional status	ADR, AE, AE to discontinuation, Serious AE	CT-P13 was well tolerated in patients who maintained the treatment after 54 weeks and in patients who Switched to CT-P13 after 54 weeks of IFX [reference product] treatment. The study also demonstrated a stable clinical efficacy of CT-P13 in RA patients. (p. 237)
Smolen *et al.*,	No info	No	ACR20, ACR50, ACR70,	ADAb, NAb in ADAb-positive	Not reported	Functional status	AE, Tx-emer. special interest, Serious AE,	SB2 [biosimilar] maintained similar efficacy, safety and immunogenicity with

First author, year	Study name	Switch	Clinical efficacy	Immunogenicity	PK/PD	PROM	Safety	Authors' conclusion (in abstract/summary)
2017[125]			CDAI, DAS28-ESR, Radiologic damage, SDAI				Tx-emer. AE	INF [reference product] up to 54 weeks in patients with moderate to severe RA. Radiographic progression was comparable at 1 year. (p. 1771)
Takeuchi *et al.*, 2015[126]	No info	No	ACR20, ACR50, ACR70, CDAI, DAS28-CRP, DAS28-ESR, EULAR response, SDAI	ADAb, NAb in ADAb-positive	AUC, C avg, C max, C min/trough, Clearance, MRT, PTF, T max, Half life, V dss	Functional status	AE, AE to discontinuation, Serious AE	CT-P13 [biosimilar] and IFX [reference product], administered at a dose of 3 mg/kg in combination with MTX to active RA patients, were pharmacokinetically equivalent and comparable in efficacy and safety. (p. 817)
Lila *et al.*, 2019[123]	LIRA	No	ACR/EULAR remission, ACR20, ACR50, ACR70, CDAI, DAS28-CRP, Radiologic damage, SDAI	ADAb	Not reported	HRQoL	AE, Serious AE, Tx-emer. AE, Tx-emer. severe AE, Severe AE	No explicit conclusion statement in the abstract

Abbreviations: ACR, American College of Rheumatology; ADAb, Anti-Drug Antibody; ADR, Adverse Drug Reaction; AE, Adverse Event; anti-CCP, Anticyclic Citrullinated Peptide; AUC, Area Under Curve; Cavg/max/min or trough, average/maximum/minimum serum concentration; CDAI; Clinical Disease Activity Index; CRP, C-Reactive Protein; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; EULAR, European League Against Rheumatism; HRQoL, Health-Related Quality of Life; PD, Pharmacodynamics; PK, Pharmacokinetics; PROM, Patient-Reported Outcome Measures; PTF, Peak-to-Trough Fluctuation Ratio; RAID, Rheumatoid Arthritis Impact of Disease; RCT, Randomized Controlled Trial; SDAI, Simplified Disease Activity Index; SJC, Swollen Joint Count; TJC, Tender Joint Count; T max, time to maximum serum concentration; Tx, Treatment; Vdss, Volume of Distribution Steady-State Method; WPAI, Work Productivity and Activity Impairment Questionnaire.

Note: In authors' conclusions, we spelled out explanations and added explanations of which term referred to the infliximab reference product and biosimilar, respectively, in square brackets (as the abbreviations used by study authors were often rather idiosyncratic).

8.1.3 Effectiveness and safety as well as PK/PD, PROMs, immunogenicity and treatment discontinuation outcomes in real-world settings

8.1.3.1 Evidence table for RWE studies

Fourteen RWE studies were identified as relevant for this scoping report (Table 10).[117 132–144]

CoI and funding: Not all studies reported on CoI and study funding. Where such information was available, most studies had at least one author who reported a CoI (7 studies) and had received some kind of funding from the pharmaceutical industry (5 studies).

Countries, settings, perspectives: Real-world evidence studies were eligible only if conducted in certain countries (see 7.1.2). Of the included studies, four were performed in Denmark and three in the Netherlands, with the remainder from Finland, France, Italy, Spain, and the UK. No study was identified for Switzerland. Most studies were set in hospitals and other medical facilities while three studies used register data. Studies were split evenly between prospective and retrospective studies.

Indications: One study was conducted in an RA-only population.[136] The remaining studies included several inflammatory or rheumatic diseases, in particular axial spondyloarthritis (AxSpa), Morbus Crohn, PsA, psoriasis, and UC. Not all studies reported patient characteristics and outcomes separately by disease. For Table 10, we extracted data for individuals with RA if reported separately though we note that sample sizes in general and RA-specific samples in particular were frequently small.

Switch, arms: Almost all RWE studies assessed switching from the infliximab reference product to infliximab biosimilar (the reverse direction was not assessed systematically but merely reported as part of adverse events, i.e. if patients were switched back to the reference product after biosimilar failure). Studies differed in how they assessed switch. Eight single-arm studies included patients who switched to infliximab biosimilar, with patients serving as their own control, i.e. comparisons were done versus baseline. Another study compared infliximab biosimilar with certolizumab pegol and abatacept, from which we considered only the infliximab arm relevant, thereby turning this study, for our purposes, into a “single-arm” study.[136] Two studies compared patients initiating treatment with or switching to infliximab biosimilar, in one case supplemented by an additional historic cohort of patients receiving the infliximab reference prepration.[134 142] The remaining studies compared reference product with biosimilar, in both switching and infliximab-naïve patients.

Follow-up time, sample size, age, and sex: Follow-up periods range from 24 weeks to 2 years. Sample sizes, as mentioned above, were frequently small and included less than 50 individuals. However, there were also six studies with 200 individuals or more.[134–136 140–142] With regard to age- and sex-related patient eligibility criteria (actual results on age and sex were not extracted at the scoping stage), about half of studies specified age to be “adults”. No study specified sex as part of its eligibility criteria.

Primary endpoints, subgroup analyses: Not all studies specified an explicit primary study endpoint or outcome. Those that did specified therapy duration (measured by drug retention)[133 138 140 142], effectiveness (in particular DAS-28)[117 144], safety (adverse drug reactions)[141], PK (serum drug concentrations), immunogenicity (ADAbs)[134], and nocebo effect (measured as unexplained unfavourable outcomes)[132] outcomes as their primary outcomes. Few studies reported on subgroup analyses. Those that did conducted analyses by, among others, prior infliximab treatment and baseline disease activity status.

Table 10 Characteristics of included RWE studies

First author, year	CoI for at least one author	Industry funding	Countries	Setting	Perspective	Indications	Switch assessed	Arms	Follow-up (weeks)	Total sample size	Age (years) eligible	Primary endpoint	Subgroups
Avouac *et al.*, 2018[133]	No info	No info	France	Hospital	Prospective	AxSpA, Crohn, RA, UC, Uveitis, Other	Yes	Switched to biosimilar	34	31	Adult	Drug retention	No info
Boone *et al.*, 2018[132]	Yes	No info	Netherlands	Hospital	Prospective (some data retrieved retrospectively)	AS, Crohn, PsA, RA, UC	Yes	Switched to biosimilar	52	9	No info	Unexplained unfavourable effect	No info
Glintborg *et al.*, 2018[134]	No info	Yes	Denmark	Hospital	Prospective	AxSpA, PsA, RA	Yes	Switched to biosimilar versus biosimilar in INX-naive	52	546	Adult	ADAb	Switchers; naive
Glintborg *et al.*, 2017[135]	Yes	Yes	Denmark	Register	Retrospective	AxSpA, PsA, RA	Yes	Switched to biosimilar	52	403	Adult	No primary endpoint specified	Previous infliximab treatment; baseline remission status; withdrawn patients
Grøn *et al.*, 2019[136]	Yes	No info	Denmark	Register	Retrospective	RA	No	Biosimilar (certolizumab pegol and abatacept arms ignored)	52	225	Adult	Not applicable	Comorbidity; seropositive status; DAS28
Holroyd *et al.*, 2018[137]	Yes	No info	United Kingdom	Hospital	Retrospective	AS, PsA, Ra, Other	Yes	Switched to biosimilar	53	59	No info	No primary endpoint specified	No info
Layegh *et al.*, 2019[138]	No info	No info	Netherlands	Hospital/outpatient	Retrospective	PsA, RA	Yes	Switched to biosimilar	104	45	Adult	Drug retention	No info
Nikiphorou *et al.*, 2019[140]	Yes	Yes	Finland	Hospital	Retrospective	AS, IBD, JIA, PsA, RA, REA, SpA, Other	Yes	Reference product versus biosimilar (switch and naive)	104	395	No info	Drug retention	Timing of biosimilar initiation
Nikiphorou *et al.*, 2015[139]	No	Yes	Finland	Hospital	Prospective	AS, JIA, PsA, RA, REA	Yes	Switched to biosimilar	48	15	Adult	No primary endpoint specified	No info
Scavone *et al.*, 2018[141]	No	No	Italy	Register	Retrospective	Crohn, Pso, RA, SpA, UC	No	Reference product versus biosimilar	104	459	No info	ADR	No info

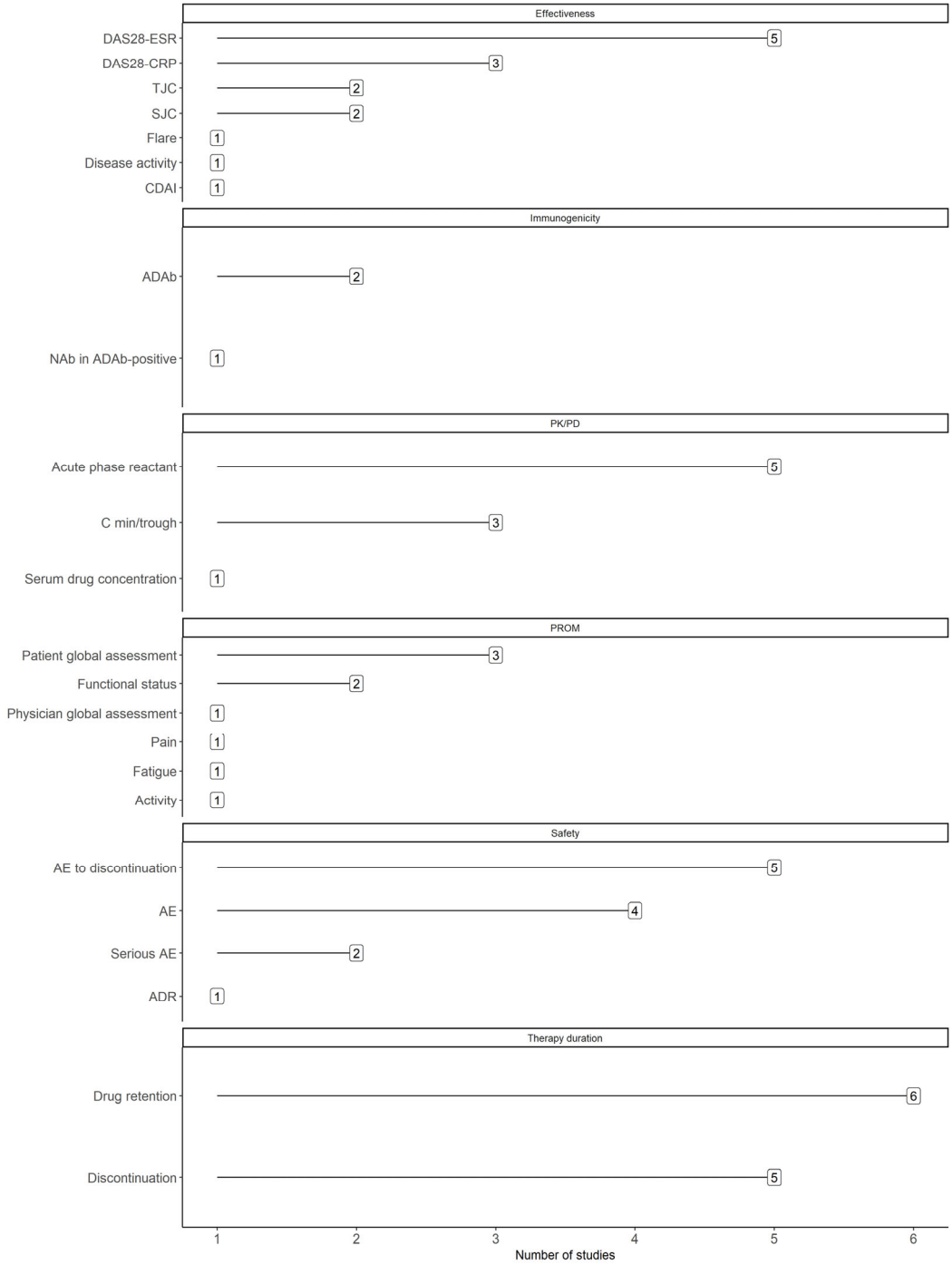
First author, year	CoI for at least one author	Industry funding	Countries	Setting	Perspective	Indications	Switch assessed	Arms	Follow-up (weeks)	Total sample size	Age (years) eligible	Primary endpoint	Subgroups
Scherlinger *et al.*, 2018[142]	Yes	No info	France	Hospital	Prospective	AS, PsA, RA	Yes	Switched to biosimilar versus biosimilar in INX-naive versus historic reference product cohort	33	200	No info	Drug retention	No info
Schmitz *et al.*, 2017[143]	No	No	Netherlands	Hospital	Prospective	AS, PsA, Pso, RA, SpA, Other	Yes	Switched to biosimilar	52	14	Adult	No primary endpoint specified	No info
Tweehuysen *et al.*, 2018[117]	Yes	No info	Netherlands	Hospital	Prospective	AS, PsA, RA	Yes	Switched to biosimilar	24	75	Adult	DAS28-CRP	No info
Vergara-Dangond *et al.*, 2017[144]	No	Yes	Spain	Hospital	Retrospective	AS, PsA, RA	Yes	Reference product versus switched to biosimilar	32	13	No info	DAS28	No info

Abbreviations: ADAb, Anti-Drug Antibody; ADR, Adverse Drug Reaction; AS, Ankylosing Spondylitis; AxSpA, Axial Spondyloarthritis; CoI, Conflict of Interest; Crohn, Morbus Crohn; CRP, C-Reactive Protein; DAS, Disease Activity Score; IBD, Inflammatory Bowel Disease; INX, Infliximab; PsA, Psoriatic Arthritis; Pso, Psoriasis; RA, Rheumatoid Arthritis; SpA, Spondyloarthritis; UC, Ulcerative Colitis.

8.1.3.2 Findings on effectiveness, safety, PK/PD, PROMs, immunogenicity and therapy duration outcomes from RWE studies

Outcomes in all domains were reported by RWE studies (Figure 4).

Figure 4 Outcomes from RWE studies



Source: Own calculations.
Abbreviations: ADAb, Anti-Drug Antibody; ADR, Adverse Drug Reaction; AE, Adverse Event; CDAI, Clinical Disease Activity Index; CRP, C-Reactive Protein; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; NAb, Neutralising Antibody; PD, Pharmacodynamics; PK, Pharmacokinetics; PROM, Patient-Reported Outcome Measures; RWE, Real-World Evidence; SJC, Swollen Joint Count; TJC, Tender Joint Count.

Effectiveness: DAS28 was the most frequently reported effectiveness measure (available based on CRP and ESR), with all eight studies reporting on effectiveness providing DAS28 (Table 11). Other effectiveness outcomes were less frequent and reported by at most two studies.

Immunogenicity: Data on ADAb or neutralising antibodies were reported by three studies.

PK/PD: Five studies reported on acute phase reactants, three on minimum serum concentrations, and one study on serum drug concentrations in general.

*PROM*s: Three studies reported on patient global assessment, with two of them also providing data on functional status. Pain, fatigue, and self-reported disease activity were reported by a single study.[139]

Safety: Safety data were reported relatively frequently, including any AE, serious AE, and in particular AE leading to discontinuation of treatment. Data on adverse drug reactions were reported by a pharmacovigilance-based study.[141]

Therapy duration: Data on drug retention or therapy discontinuation were the most frequently reported outcome and provided by all but three studies.

Assessment of RWE study-based evidence: The RWE studies identified for assessments of infliximab biosimilars in patients with RA in the target countries were found to be heterogeneous in their design. In addition, a substantial proportion of studies relied on small sample sizes. Specific outcomes, with the exception of DAS28, were reported by only few studies each. In light of these issues and of methodological challenges regarding synthesis of non-randomised studies[145], a quantitative synthesis of RWE results is unlikely to be feasible and worthwhile.

However, we would suggest to synthesize RWE studies narratively in the respective outcome domains. Notably, authors' conclusions for these RWE studies generally suggested that infliximab reference product and biosimilar were comparable in clinical practice with regard to effectiveness and safety (Table 11). However, some authors also reported that infliximab biosimilar was associated with worse PROMs and higher treatment discontinuation, which was frequently attributed to nocebo effects. It is for the discussion of nocebo effects that we see the main value of RWE studies in an HTA, in the form of a narrative synthesis in conjunction with data from RCTs and existing reviews.[116 146 147]

Table 11 Outcomes by RWE study

First author, year	Switch	Effectiveness	Immunogenicity	PK/PD	Therapy duration	Safety	PROM	Authors' conclusion (in abstract/summary)
Avouac *et al.*, 2018[133]	Yes	DAS28-ESR, Disease activity, SJC, TJC	Not reported	Acute phase reactant, C min/trough	Drug retention	AE to discontinuation, Serious AE	Not reported	No changes in drug trough levels or objective parameters were observed after the systematic switch to biosimilar infliximab in a real clinical practice setting. Only changes in patient-reported outcomes were observed, suggesting attribution effects rather than pharmacological differences. (p. 741)
Boone *et al.*, 2018[132]	Yes	DAS28-ESR	NAb in ADAb-positive	Acute phase reactant, C min/trough	Discontinuation	Not reported	Not reported	In inflammatory bowel disease and rheumatological patients, similar effectiveness and safety were demonstrated on the transition into infliximab biosimilar. In our series, patient empowerment and registration of treatment outcomes delineated biosimilar transition, an approach that hypothetically could reduce nocebo response rates which are relevant to account for regarding biosimilar implementation. (p. 655)
Glintborg *et al.*, 2018[134]	Yes	Not reported	ADAb	Serum drug concentration	Discontinuation	Not reported	Not reported	No explicit conclusion statement in the abstract
Glintborg *et al.*, 2017[135]	Yes	DAS28-CRP, Flare	Not reported	Acute phase reactant	Drug retention	AE	Functional status, Patient global assessment	In 802 arthritis patients treated with INX [reference product] for median >6 years, a nationwide non-medical switch to CT-P13 [biosimilar] had no negative impact on disease activity. Adjusted 1-year CT-P13 retention rate was slightly lower than for INX in a historic cohort. (p. 1426)
Grøn *et al.*, 2019[136]	No	DAS28-CRP, CDAI	Not reported	Not reported	Drug retention	Not reported	Not reported	The surrogate randomization procedure enabled head-to-head comparisons of CZP [certolizumab pegol], ABA [adalimumab], and CT-P13 [infliximab biosimilar]. Although some differences in estimated effectiveness were observed across drugs, confidence intervals were wide and statistical significance was not reached. (p. 1997)
Holroyd *et al.*, 2018[137]	Yes	Not reported	Not reported	Not reported	Discontinuation	AE to discontinuation	Not reported	No explicit conclusion statement in the abstract
Layegh *et al.*, 2019[138]	Yes	DAS28-ESR	Not reported	Not reported	Drug retention	Not reported	Not reported	In our population, 87% of patients continued Remsima [biosimilar] during the follow-up period of approximately 2 years. Three patients restarted Remicade [reference product], while retaining stable DAS28-ESR. (p. 869)
Nikiphorou *et al.*, 2019[140]	Yes	Not reported	Not reported	Not reported	Drug retention	AE to discontinuation	Not reported	IB [biosimilar] was well-tolerated and comparable to IO [reference product], with no additional safety signals identified. The results suggest superior survival of IB over IO over the first 2 years. (p. 55)
Nikiphorou *et al.*, 2015[139]	Yes	Not reported	Not reported	Acute phase reactant	Discontinuation	Not reported	Physician global assessment, Activ-	The clinical effectiveness of INB [biosimilar] in both PROs and disease-activity measures was comparable to INX [reference product] during the first year of

First author, year	Switch	Effectiveness	Immunogenicity	PK/PD	Therapy duration	Safety	PROM	Authors' conclusion (in abstract/summary)
							ity, Fatigue, Functional status, Pain, Patient global assessment	switching, with no immediate safety signals. Subjective reasons (negative expectations) may play a role among discontinuations of biosimilars. Larger patient numbers and longer follow-up are necessary for confirming this clinical experience. (p. 1677)
Scavone *et al.*, 2018[141]	No	Not reported	Not reported	Not reported	Not reported	ADR	Not reported	Our study demonstrates that, along with a rapid increase in the utilization of infliximab biosimilars across Italy, there was also an increase in reporting ADRs induced by infliximab biosimilars. Of the reported ADRs, 7.4% were considered preventable. In adjusted analyses, infliximab biosimilars were shown to have an increased probability of being reported as suspected drugs in infusion reactions and a decreased probability of being reported as suspected drugs in cases of lack of efficacy or infection. Considering the potential advantages offered by the utilization of biosimilars in clinical practice, we believe that the use of biosimilars, including those of infliximab, should be supported. In order to achieve this aim, increased knowledge on safety and efficacy of biosimilar drugs should be obtained from real world clinical practice. (p. 607)
Scherlinger *et al.*, 2018[142]	Yes	Not reported	Not reported	Not reported	Drug retention	AE, AE to discontinuation	Not reported	Retention rate was lower after switching from OI [reference product] to CT-P13 [biosimilar] compared to our control cohorts. However, this difference faded after excluding patients without objective clinical activity, suggesting a reluctance of patients to the switch and a negative perception of the biosimilar. (p. 561)
Schmitz *et al.*, 2017[143]	Yes	DAS28-ESR	Not reported	Not reported	Discontinuation	Not reported	Not reported	In conclusion, no pharmacokinetic or clinical differences were found between INX [reference product] and INB [biosimilar] in our diverse rheumatic cohort. TDM [therapeutic drug monitoring] is a helpful tool to monitor patients switching from INX to INB. (p. 2129)

First author, year	Switch	Effectiveness	Immunogenicity	PK/PD	Therapy duration	Safety	PROM	Authors' conclusion (in abstract/summary)
Tweehuysen *et al.*, 2018[117]	Yes	DAS28-CRP, SJC, TJC	ADAb	Acute phase reactant, C min/trough	Not reported	AE, Serious AE	Patient global assessment	In our cohort, one-fourth of patients discontinued CT-P13 [biosimilar] during 6 months of follow-up, mainly due to an increase in the subjective features of the tender joint count and the patient's global assessment of disease activity and/or subjective AEs, possibly explained by nocebo effects and/or incorrect causal attribution effects. (p. 60)
Vergara-Dangond *et al.*, 2017[144]	Yes	DAS28-ESR	Not reported	Not reported	Not reported	AE, AE to discontinuation	Not reported	CT-P13 [biosimilar] was equally effective as infliximab RP [reference product] in this real-world study. CT-P13 is a valid, lower-cost alternative for patients currently receiving RP. (p. 481)

Abbreviations: ADAb, Anti-Drug Antibody; ADR, Adverse Drug Reaction; AE, Adverse Event; C min/trough, minimum serum concentration; CRP, C-Reactive Protein; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; Nab, Neutralizing Antibody; PD, Pharmacodynamics; PK, Pharmacokinetics; PROM, Patient-Reported Outcome Measures; RWE, Real-World Evidence; SJC, Swollen Joint Count; TJC, Tender Joint Count.
Note: In authors' conclusions, we spelled out explanations and added explanations of which term referred to the infliximab reference product and biosimilar, respectively, in square brackets (as the abbreviations used by study authors were often rather idiosyncratic).

8.1.4 Costs, cost-effectiveness and budget impact outcomes

8.1.4.1 Evidence table for health economic analyses

Eleven health economic studies were identified as relevant for this scoping report (Table 12).[134 148–157]

CoI and funding: All eleven studies reported on CoI, with seven studies reporting at least one author with a CoI. Study funding was reported for ten studies, with six studies having received some kind of funding from the pharmaceutical industry.

Countries: HE studies were eligible only if conducted in certain countries (see Section 7.1.2). Two studies estimated the budget impact for five countries.[153 154] Of included studies, four were performed for the UK and three for Italy and the US, with the remainder for Belgium, Canada, Denmark, France, Germany, Netherlands, and Spain. No study was identified for Switzerland in the searches. Please note that a Swiss budget impact analysis for biosimilars has been recently published by Kobler *et al.*[158] However, the report was published in March 2020 – after searches had been implemented – and so was not formally included in our search results for the scoping result (but will of course be considered in a full HA).

Types of health economic studies: No full economic evaluation study or cost-minimization analysis was identified. Six studies were BIAs and four studies costing studies. Costing studies were mainly retrospective studies. One study reported on resource utilization without assigning unit costs.[159] Therefore, this study did not report an outcome in monetary units.

Perspective: Four studies were conducted from a healthcare system perspective. Another four studies investigated a healthcare payer perspective while two studies also investigated a healthcare provider perspective. Three studies used a health insurance perspective, of which one also reported costs from a patient perspective (out-of-pocket costs).

Time horizon: The time horizon of the HE analyses ranged from 0.25 up to 5 years.

Indications: Three studies were conducted in an RA-only population. The remaining studies included several inflammatory or rheumatic diseases, in particular AS, AxSpA, Morbus Crohn, IBD, PsA, psoriasis, and UC. In these multi-disease studies, results were generally not reported per single disease.

Table 12 Study characteristics of included health economic studies

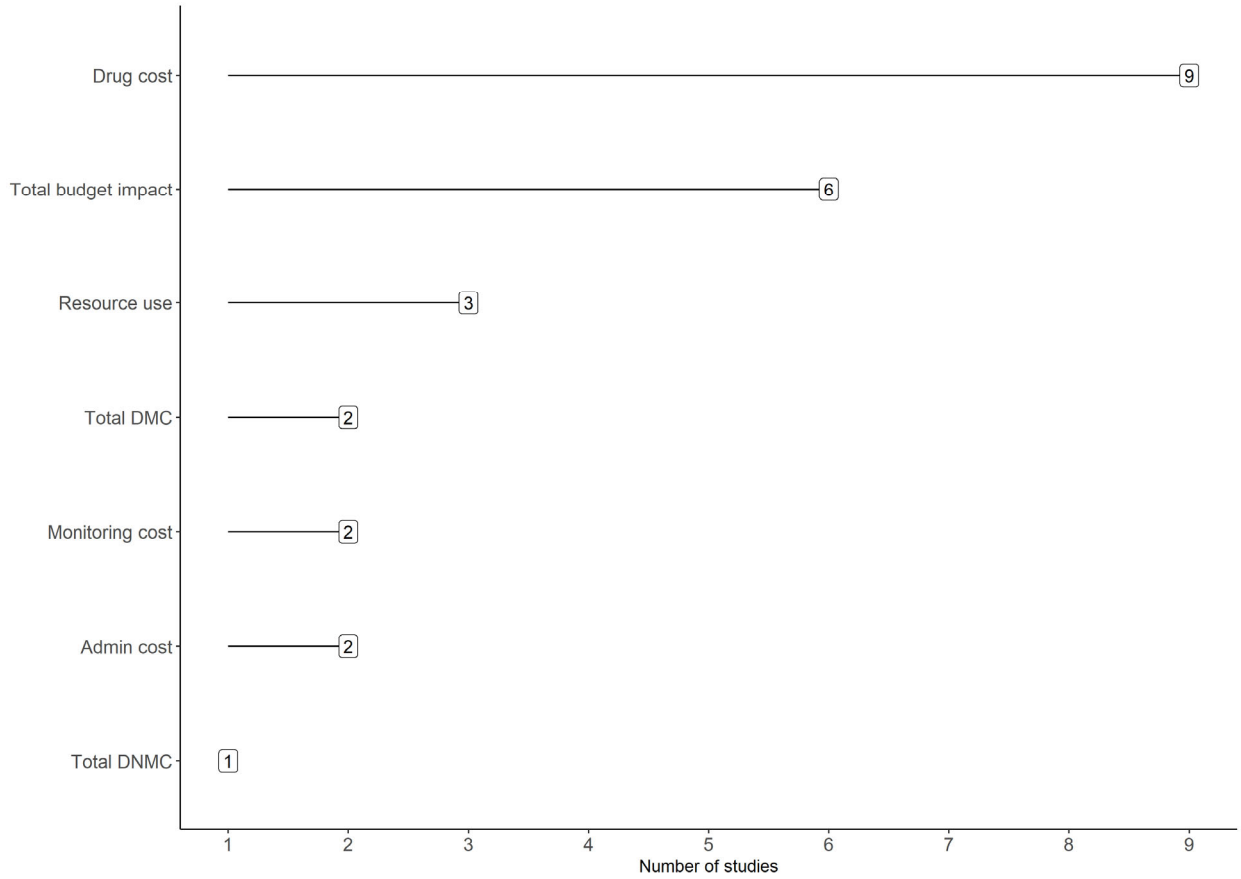
First author, year	CoI for at least one author	Industry funding	Countries	Full economic evaluation	Type of HE study	Perspective	Time horizon (years)	Indications	Subgroups
Aladul *et al.*, 2019[148]	No	No	United Kingdom	No	BIA	Healthcare system (NHS)	3	AS, Crohn, PsA, RA, UC	No info
Aladul *et al.*, 2017[149]	No	No	United Kingdom	No	Costing	Healthcare system (NHS)	3	AS, PsA, RA	No info
Beck *et al.*, 2017[150]	Yes	No info	France	No	BIA	Health insurance (CNAMTS)	1	RA	Alsace and France
Curtis *et al.*, 2019[151]	Yes	No	United States	No	Costing	Healthcare insurance (Medicare)	1.5	RA	No info
Gibofsky *et al.*, 2019[152]	Yes	Yes	United States	No	BIA	Healthcare provider/payer	0.25	AS, Crohn, PsA, Pso, RA, UC	No info
Glintborg *et al.*, 2018[159]	Yes	Yes	Denmark	No	Costing (resource use)	Healthcare system	0.5	AxSpA, Pso, RA	No info
Jha *et al.*, 2015[153]	Yes	Yes	Belgium, Germany, Italy, Netherlands, United Kingdom	No	BIA	Healthcare payer	1	AS, Crohn, PsA, Pso, RA, UC	Country
Kanters *et al.*, 2017[154]	Yes	Yes	France, Germany, Italy, Spain, United Kingdom	No	BIA	Healthcare payer	5	AS, IBD, RA	Country
Lucioni *et al.*, 2015[155]	No	Yes	Italy	No	BIA	Healthcare system (NHS)	5	AS, Crohn, PsA, Pso, RA, UC	Infliximab-naive, and switch population; by indication
Mansell *et al.*, 2019[157]	No	Yes	Canada	No	Costing	Healthcare provider/payer	2	Not applicable	Province
Yazdany *et al.*, 2018[156]	Yes	No	United States	No	Costing	Health insurance (Medicare), patient (OOP)	1	RA	No info

Abbreviations: AS, Ankylosing Spondylitis; AxSpA, Axial Spondyloarthritis; BIA, Budget Impact Analysis; CNAMTS, Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés; CoI, Conflict of Interest; Crohn, Morbus Crohn; IBD, Inflammatory Bowel Disease; OOP, Out-Of-Pocket; PsA, Psoriatic Arthritis; Pso, Psoriasis; RA, Rheumatoid Arthritis; UC, Ulcerative Colitis.

8.1.4.2 Findings on costs, cost-effectiveness and budget impact outcomes

Studies reported several health economic outcomes (Figure 5).

Figure 5 Outcomes from health economic studies



Source: Own calculations.
Abbreviations: DMC, Direct Medical Costs; DNMC, Direct Non-Medical Costs.

Drug cost: Nine out of eleven studies investigated drug costs. The two remaining studies investigated healthcare service resource use without assigning unit costs[159] and extra time spent by physicians as well as laboratory tests and other procedures required due to non-medical switching[152] (Table 13).

Total budget impact: Six studies reported total budget impact. However, this outcome was estimated differently between studies. Three studies assumed that the main relevant difference would be due to drug costs. Two studies also included differences due to drug administration and monitoring[152 154] and one study also included direct non-medical costs based on transport expenses[150].

Resource use: Resource utilization was reported separately in three studies.[151 152 159]

Assessment of health economic evidence: The health economic studies identified for assessments of infliximab biosimilars in patients with RA in target countries were either BIAs or costing studies. No full

health economic evaluation was identified (they are more frequently used when comparing different substances or drug classes[160–162]). Although different cost perspectives were used, most studies analysed drug costs, and authors' conclusions generally suggested substantial cost savings associated with increased use of biosimilars (Table 13). While one study reported considerable short-term switching costs due to increased drug administration and monitoring[152], another study found only marginal changes with no clinically relevant increase in resource use after switching[159]. Consequently, a BIA focusing on drug, administration, and monitoring costs in Switzerland could be considered, similar to or based on the analysis by Kobler *et al.*[158]

Table 13 Outcomes by health economic study

First author, year	Outcomes	Authors' conclusion (in abstract/summary)
Aladul *et al.*, 2019[148]	Drug cost, Total budget impact	The introduction of new infliximab, etanercept and adalimumab biosimilars will be associated with considerable cost savings and have a substantial favourable impact on the UK NHS budget. The number of biosimilars and time of entry of [sic] is critical to create competition which will result in maximum cost savings. (p. 310)
Aladul *et al.*, 2017[149]	Drug cost	The introduction of bDMARDs biosimilars has resulted in considerable cost savings to the NHS, with the branded products reducing their prices in response to the availability of less expensive biosimilars and competition between the biosimilars themselves. Our results also suggest that when a biosimilar is available for a directly comparable branded molecule, price is the key influencing factor in the prescribing of a specific product. (p. 533)
Beck *et al.*, 2017[150]	Drug cost, Total budget impact, Total DMC, Total DNMC	The study showed a positive financial impact of introducing biosimilar infliximab for the treatment of RA patients in France. Such savings could contribute to improved patient care by allowing more patients to be treated without more money being spent. (p. 85)
Curtis *et al.*, 2019[151]	Drug cost, Resource use	Despite frequent dose escalation with infliximab that often increase its dose by threefold or more, the savings from the current price of its biosimilar substantially offsets the costs of an alternative infused TNFi [TNF-alpha inhibitor] biologic for which no biosimilar is available. (p. 1)
Gibofsky *et al.*, 2018[152]	Admin cost, Monitoring cost, Resource use, Total budget impact, Total DMC	Originator-to-biosimilar NMS [non-medical switching] in stable patients with autoimmune conditions could result in considerable switching costs for both providers and payers. (p. 97)
Glintborg *et al.*, 2018[159]	Resource use	Changes were marginal with no clinically relevant increase in use of outpatient health care resources 6 months after compared with 6 months before mandatory switch from originator to biosimilar infliximab. (p. 1)
Jha *et al.*, 2015[153]	Drug cost, Total budget impact	The introduction of Remsima [infliximab biosimilar] could lead to considerable drug cost-related savings across the six licensed disease areas in the five European countries. (p. 743)
Kanters *et al.*, 2017[154]	Admin cost, Drug cost, Monitoring cost, Total budget impact	This study has shown that only when price reductions are large enough (i.e., 50% or more), physicians indicated that they will prescribe biosimilars. Policy makers should ensure substantial price reductions and stimulate physicians to use biosimilar products, to obtain savings in healthcare budgets. (p. 1)
Lucioni *et al.*, 2015[155]	Drug cost, Total budget impact	The results from the analysis show (in the base case) that the availability of the biosimilar would provide overall annual savings over EUR 16 million to the NHS in 2019, while the cumulated savings in the five years period would be no less than EUR 47 million. The sensitivity analysis highlights that such favourable results would be even more substantial, to the extent that switching from originator to biosimilar could be safely recommended. (p. 78)
Mansell *et al.*, 2019[157]	Drug cost	The overall use of biosimilar drugs in Canada is low. Policy makers, healthcare providers, and patients need to be informed of potential savings by increased use of biosimilars, particularly in an increasingly costly healthcare system. (p. 1)
Yazdany *et al.*, 2018[156]	Drug cost	No explicit conclusion statement in the abstract

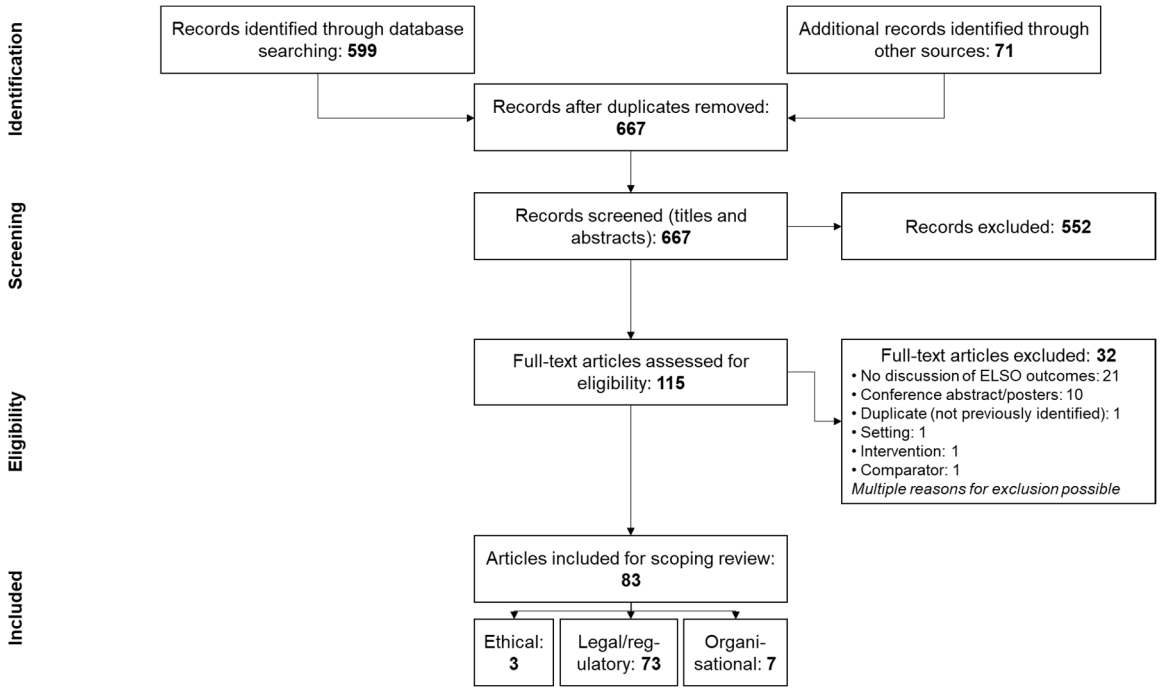
Abbreviations: bDMARDs, Biological Originator Disease-Modifying Anti-Rheumatic Drugs; DMC, Direct Medical Costs; DNMC, Direct Non-Medical Costs; NHS, National Healthcare System; NMS, Non Medical Switch; RA, Rheumatoid Arthritis.

8.2 Evidence base pertaining to ethical, legal, social and organizational issues

8.2.1 PRISMA flow diagram

The search for evidence on ELSO outcomes yielded 599 hits from literature databases and 71 hits from other sources (Figure 6).

Figure 6 PRISMA flow diagram for ELSO issues search



Source: Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses..[119]
Abbreviation: ELSO, Ethical, Legal, Social, Organizational; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Of the 667 unique hits, 552 were excluded during title-abstract-screening. Of the remaining 115 articles whose full-texts were screened, 32 were excluded, mostly because they did not discuss ELSO outcomes or because they were conference abstracts/posters (see Section 12.5.2). Eighty-three articles were retained for the scoping report, including 73 studies discussing, reviewing, or reflecting on legal/regulatory issues, 7 discussing organizational issues, and 3 discussing ethical issues.

8.2.2 Evidence table for studies reporting on ELSO outcomes

Characteristics of the studies reporting on ELSO outcomes are shown in Appendix table 7.

CoI and funding: Not all studies reported on CoI and study funding or studies were publications by state agencies where CoI and study funding where not applicable. In 18 of the 39 studies for which CoI information was available and CoI applicable, at least one study author reported a CoI. The corresponding number for study funding by the pharmaceutical industry was 13 out of 25 studies.

Study types: We grouped studies/reports into different types. Forty-one studies were reviews (usually of regulatory or legal procedures/frameworks) and 22 were guidance documents or position statements. The remainder were explanatory articles, articles reporting on real-world experience or policy plans, and general reflections (within the ELSO domains) on biosimilars.

Countries: The US and Europe, on their own or in comparison, and multinational comparisons were by far the most frequently reported settings (55 articles/reports). For individual countries in and beyond Europe (with the exception of the US), fewer studies/reports were identified.

We would like to reiterate at this point that the aim of searching for and reviewing studies within the ELSO domains was *not* (and would not be for a full HTA) an exhaustive review of the literature. Instead, we used these searches to identify important sources for target countries and retrieve sufficient information on regulatory and reimbursement frameworks, ethical, legal, and social issues. In addition to the information identified from the literature, we also relied on domain-specific knowledge to raise important ethical and legal issues for Switzerland that should be reviewed in depth in a full HTA.

8.2.3 Findings and suggested questions regarding ethical issues

Findings on ethical issues from the literature search were sparse. In addition to a study discussing the usefulness of and need for animal studies in the context of biosimilar development[163], we identified two studies discussing ethical implications of non-medical switching from reference products to biosimilars.[164 165] Both studies used as their premise the uncertainty around the safety of non-medical switches and argued that, despite evidence suggesting that biosimilars in general and switches in particular were safe and effective, this uncertainty would need to be balanced with patients', physicians', and society's interests. Specifically, both papers pointed out that society had a justified interest in the cost containment achievable with biosimilars while patients and physicians had a justified interest in the freedom to decide in the best interest of the specific patient, e.g. if on remission with a reference product. The authors suggested several approaches to help balance these interests, ranging from reducing prices for originator biologics (after patent expiry) to the extent that biosimilar production was no longer profitable[165] to a "robust and thorough disclosure of relevant risks, benefits and reasonable alternatives"[164].

In addition to these literature findings, we formulated a range of questions that can be investigated in a full HTA.

According to the HTA Core Model, "[e]thical analysis aims to provide a thorough understanding of norms and values that need to be taken into account during the HTA and in the decision-making process"[105]. As we are convinced that no single method for ethical analysis is likely to be sufficient to fully address the moral questions of applying a health technology[166], we will use the axiological approach in this scoping review. The axiological – or Socratic – approach is based on a series of questions and answers, with the intention to stimulate critical thinking and to draw out underlying presuppositions, and is considered a valid methodological option in HTA.

The "Hofmann catalogue"[108 109] with 33 questions designed to identify the characteristics of a health technology, the involved stakeholders, and the relevant moral questions is a widely-used implementation of the axiological approach.[167–169] We are aware that the catalogue of 33 morally relevant questions presented by Hofmann is "not exhaustive […] moral questions […] have to be added, depending on the specific technology or its particular use"[109]. Yet, we will address selected questions from the catalogue at the scoping stage to raise awareness for the underlying ethical concerns pertinent to the substitution of the infliximab reference product with its biosimilars for the treatment of patients with RA. We will not give answers in the sense of normative solutions. Please note that numbering of the questions outlined below follows that in Hofmann's paper[109].

Q1: What are the morally relevant *consequences* of the implementation of the technology?

On the basis of current evidence, which, however, will have to be shown in a full HTA, we assume that there is equivalent effectiveness, safety, and quality for the infliximab reference product and biosimilars in patients with RA.[100] Even for the reference product, it is obvious that no lot is 100% similar to the next one as they are produced by living organisms.[79 80 170] Biosimilars may deviate from the reference product only as much as different lots would deviate from each other.[78] In summary, treatment initiation with or switching to biosimilars *per se* are not deemed to pose a problem endangering or harming patients.

Against this background we will confine the ethical analysis to questions of non-medical switching between infliximab reference product and biosimilars for the treatment of patients with RA. Relevant moral questions are as to when, how, for which patients, at what point in time switching could be done and by what kind of communication this action should be accompanied.

Q10: Can the use of the technology in any way challenge relevant law?

This question is considered in Section 8.2.4.

Q12: Are there any related technologies that have turned out be morally challenging?

We acknowledge that substitution with generics is not equivalent to substitution with biosimilars, but the former can be considered a technology with some comparable moral challenges. There is no specific literature on the ethical problems of switching from infliximab reference product to biosimilars (or vice

versa) in RA so one needs to explore the general ethical questions of biologics and biosimilars in a first step and then analyse whether similar ethical questions and possible solutions occur in comparable questions, e.g. substitution with generics.

Q14: How does the implementation of the technology affect the distribution of health care?

As stated by Hofmann, "[m]any technologies imply substantial costs, sometimes covered with resources from other areas"[109]. If financial resources can be saved by substituting reference products, this may help the healthcare system free resources for other patients (also see Q33 below).[82]

Q15: How does the technology contribute to or challenge professional autonomy?

The issue of professional autonomy is raised by some authors in the context of the substitution of biologics. One needs to scrutinize this argument: If the evidence strongly implies that biosimilars are neither less effective nor less safe than their reference products, then professional autonomy should not be a question in the sense that physicians should *per se* have a choice of treatment. Their autonomy should be looked at in particular cases (also see Q1), e.g. in terms of timing a switch. In addition, adherence to guidelines is not discussed under the aspect of reduced autonomy.

Therefore, the question of professional autonomy needs to be reframed: The question of overall professional autonomy does not pertain to switching *per* se on the assumption that effectiveness and safety of biosimilars are non-inferior to infliximab but to, among others, when to switch.

Q16: Can the technology harm the patient?

The available scientific evidence does not suggest, to the best of our knowledge, that switching from reference product to biosimilar will harm patients. Yet, the reference product could likewise harm the patient. In the face of nocebo effects reported under switching from reference product to biosimilar, communication and the attitude of the prescribing physician are crucial in order to minimize harm to the patients: "Patients may experience nocebo effects (worsening or incitement of symptoms that are induced by a negative attitude toward an intervention) that are only perceptible to the patient and may impact on quality of life, treatment adherence, and the cost-saving potential of biosimilars."[171] As pointed out by Kim *et al.*, "patient understanding of biosimilars is crucial for treatment success and avoiding nocebo effects. Full understanding of biosimilars by physicians and carefully considered communication strategies can help support patients initiating or switching to biosimilars"[171]. For this, the prescribers need objective patient communication material; it needs to be discussed by whom this material should be provided.

From a moral perspective, switching *per se* is not the problem, but adequate framing of the decision and inclusion of patients in decision-making are essential. This also relates to the adequate understanding of professional autonomy in the face of current evidence (also see Q15). Switching, however, should

not be performed during particularly vulnerable times in patients' lives, e.g. when patients face difficult family situations, periods of transition (job, adolescence), suffer from bereavement, or during pregnancy and early motherhood.

Q20: What are the interests of the producers of technology?

There are economic interests for both producers of reference products and of biosimilars. The problem is not specific to the question of this scoping review.

Q33: What are the moral consequences of the *scoping review*?

Patients may no longer receive the infliximab reference product, a consequence that according to our understanding of the current evidence does not seem to be problematic. Nevertheless, patients may feel that they do not receive the "best" treatment. Experts, physicians, and the public should be sensitized that communication around switching is crucial for the success of switching to or starting therapy with infliximab biosimilar.

Conclusion

The ethical challenges delineated in this scoping review are, from our perspective, the key issues to be examined and discussed in detail in a full HTA, based on a literature search (also see Droste *et al.*[167]).

8.2.4 Findings and suggested questions regarding legal and regulatory issues

A review of the literature on legal and regulatory issues concerning biosimilars for different countries is provided in Section 8.2.7. Here, we discuss legal aspects and challenges of biosimilars specifically for the Swiss context. This discussion is designed to raise legal questions that could be investigated in a full HTA.

We developed a set of questions that we consider important in the context of biosimilars from a Swiss legal perspective. We followed the objectives laid out by the HTA Core Model® for the legal domain: "The objective of the Legal Aspects (LEG) domain is to assist the HTA doers in detecting rules and regulations which need to be taken into consideration when evaluating the implications and consequences of implementing a health technology"[105]. In this framework, "the aim within LEG is not, and indeed cannot be, to give or even propose a binding legal solution to a given question. Instead, the aim is to guide the HTA doers in recognising the relevant legal questions they need to consider when evaluating the technology and providing advice for decisionmakers"[105]

Here, we discuss the legal aspects of interchangeability of biologicals. We consider several questions to guide our discussion, based on a checklist designed for the Swiss legal system.[107]

Is there an explicit legal regulation of the interchangeability of biologics in Switzerland?

No. Currently, neither the therapeutic products law nor health insurance law regulate explicitly the interchangeability of biologics (Swiss Supreme Court [SSC] decision 2C_60/2018, 31.5.19, consid. 4.2.3; Swissmedic[172]). Regulation of substitution in Swiss health insurance law (Art. 52a Krankenversicherungsgesetz [KVG]) pertains, at this time, only to (small-molecule) generics (SSC decision 2C_60/2018, 31.5.19, consid. 4.2.3; Eichenberger and Helmle[110]; Wildi[173], margin note 76). A revision to this regulation is currently under review in parliament.[174]

According to SSC decision 2C_60/2018 (31.5.19, consid 4.2.4), the decision on interchanging drugs rests with treating physicians, who have to abide by their professional duties and due diligence.

What is the legal perspective on interchangeability?

The SSC recently decided that biologic reference products and their biosimilars could not just be interchanged ("nicht ohne Weiteres gegeben") (SSC decision 2C_60/2018, 31.5.19, consid. 4.2.3). Much more restrictively, the FOPH stated flatly in 2013 that biosimilars could not be interchanged with the reference product (and with each other) due to concerns about patient safety and immunogenicity.[175] To this day, administrative practice refers to this FOPH statement.[172]

Interchangeability is not part of the regulatory approval of a biologic. Consequently, approval does not contain any statement regarding the interchangeability of the reference product with its biosimilar in an individual treated case (SSC decision 2C_60/2018, 31.5.19, consid. 4.2.3). Such a decision (i.e. about interchangeability in an individual case) rests exclusively with the treating physician, according to Swissmedic.[176]

When is interchangeability admissible from a legal perspective?

1. This question appears not to have a definitive legal answer. As discussed, according to current legal regulation, the decision about interchanging rests with treating physicians who need to consider their professional duties and due diligence (especially Art. 3 and 26 HMG; Art. 40 Medizinalberufegesetz; SSC decision 2C_60/2018, 31.5.19, consid. 4.2.4).

2. We first need to consider which legal benchmark needs to be applied to healthcare professionals' professional duties and due diligence if scientific knowledge about risks for patient safety is at least partly absent.

From a legal point of view, the following question appears to be crucial: Does the therapeutic product law-based precautionary principle (Art. 3 and 26 HMG; also see Swiss Federal Appeal Committee[177]) require that even potential dangers to patient safety which result from changes to patient medication need to be avoided as far as possible?

a) If the answer to this question is “yes”, then therapeutic product law permits healthcare professionals to change medication only if scientific evidence shows that such a change does not (or only in extremely rare cases) endanger patients due to different adverse event profiles (see Eichenberger and Helmle[178], margin note 50).
b) If the answer to this question is “no”, then risks which are only conceivable or hypothetical are no reason not to change medication. One should refrain from medication changes only if there is sufficient probability, backed up by scientific evidence, that patient safety could be in danger.

3. We also need to consider the health insurance law. It currently does not include statements regarding interchangeability and substitution of biologic drugs but requires, among others, a general assessment of cost-effectiveness (Art. 52 Paragraph 1 in conjunction with Art. 32 Paragraph 1 and Art. 43 Paragraph 6 KVG). In the legal literature on health insurance law, it is mentioned that it is at least questionable whether the originator product should be prescribed to treatment-naïve patients without further consideration or whether the use of a biosimilar or reductions in the price of originator products should not be required (see Wildi[173], Art. 52/52a KVG margin note 79). An explicit legal regulation is currently missing. The legal literature takes the position that gaps in the law should be closed by taking into account the relative cost-effectiveness principle (see Wildi[173] Art. 52/52a KVG margin note 79).

4. There is no definitive legal decision on how to proceed in case of a conflict between norms set by therapeutic product law (see second bullet point in this section) and health insurance law (see third bullet point in this section). The health insurance law currently specifies for generics (and therefore not directly applicable to biosimilars) that an insured patient does not have to bear any incremental costs if the treating physician prescribes the reference product for medical reasons (Art. 38a Paragraph 6 Krankenpflegeleistungsverordnung). This makes a therapeutic decision based on therapeutic product law feasible and helps avoid a conflict between therapeutic product and health insurance law. Lack of such an opening clause may lead to rather difficult legal questions.[179]

Additional note: Responsibility for a decision about the precautionary principle rests primarily with legislators. The relationship between the therapeutic product law-based precautionary principle (the scope of which has not been definitively settled) and the health insurance law has, from a legal perspective, not been settled. Legislators will have to consider that in particular for modern technologies, with a high potential for adverse outcomes, the – legally recognized – demand for precautionary measures by the state will grow.[180] A possible approach might be to design legal regulation according to the potential for

risk or endangerment. There would be a need to investigate, for example, if due to a) an abstract potential for risk and/or b) scientific evidence new prescriptions and switch need to be treated differently.

How is interchangeability to be evaluated in the context of therapeutic freedom?

Therapeutic freedom is based on, among others, the economic freedom specified in Art. 27 of the federal constitution, and it is a prerequisite for diligent and scrupulous professional practice (Art. 40 Medizinalberufegesetz). Therapeutic freedom implies the physician's right to refuse performing a certain treatment or to choose one among several treatment options. This also applies to dispensing and prescribing drugs.[181]

Therapeutic freedom does not hold absolutely but is restricted by the legal system (see Giger *et al.*[182], p. 11). Important direct and indirect bars are set by legal regulations on therapeutic products and health insurance. At present, these regulations do not regulate explicitly the interchangeability of biologics. Both decision and responsibility therefore rest with the treating physician. A potential risk to patient safety would exist, according to the current legal situation, in particular if an individual responsible for prescribing and dispensing medicinal products were to violate their due diligence and professional duties (SSC decision 2C_60/2018, 31.5.19, consid. 4.2.4).

The more vague the legal requirements for interchangeability, the greater the responsibility of healthcare professionals. For reasons of avoiding liability, this can lead to reluctance regarding the prescription and dispensing of biosimilars.[179] [183] A clarification can be provided by law and/or by professional guidelines.

How is interchangeability to be evaluated in the context of patient rights?

Different patient rights are relevant for the issue at hand, including:

- Patient autonomy: Patient autonomy is derived from the constitutionally guaranteed protection of personal rights and private autonomy. Patients' self-determination is safeguarded in particular by the requirement for informed consent to a (pharmaceutical) therapy. If different courses of treatment exist, the patient must be informed about them.[178]
- Equality before the law/discrimination: If a change in medication is associated with an increased risk for patient safety (see above for relevant benchmarks), then particularly vulnerable groups such as chronically ill patients must not be disadvantaged. In addition, unequal treatment – directly or indirectly – of patients must be avoided, e.g. if patients need to choose between higher risks and higher costs due to reference price systems or deductibles *that do not provide exceptions*.

What are additional legal considerations of interchangeability?

Additional legal questions that require investigation, e.g. regarding the reliability and limits of substance (international non-proprietary name)-based prescription[178] and regarding the appropriate design of traceability and pharmacovigilance ("good pharmacological practice").[184] Moreover, misguided incentives and conflicts of interest when prescribing and dispensing drugs need to be considered, e.g. with regard to incentives to generate higher profit when prescribing originator products or to the additional administrative burden when prescribing biosimilars.[158]

8.2.5 Findings on social issues

We identified no studies on social issues associated with biosimilars.

8.2.6 Findings on organisational issues

Organisational issues relate to various policies on promoting and implementing biosimilars (and they are frequently closely related to regulatory issues).

One type of studies identified in the literature mainly focus on barriers to biosimilar uptake and reasons for low market penetration of biosimilars, which range from additional workload for implementing switching to insufficient price advantages of biosimilars but also on policies designed to increase the uptake of biosimilars, which range from improved prescriber education to prescription quotas.[112 113 185–190] Another type of study focused more concretely on experiences (or plans) in countries and regions where large-scale switching to biosimilars occurred, e.g. in Denmark or British Columbia.[111 191]

8.2.7 Regulatory principles and reimbursement of biosimilars in selected countries

In this section, we present spotlight summaries of regulatory procedures for different countries, at the request of the FOPH. Specifically, we discuss regulatory and, for a subset of countries, pricing and reimbursement procedures to provide an international perspective on biosimilar regulations and reimbursement.

8.2.7.1 Regulatory/legal framework for biosimilars in selected countries

Switzerland

Key definitions: *Biosimilars* are defined by Swissmedic as "biological medicinal product[s] having sufficient similarity with a reference product authorised by Swissmedic and which refers to its [the reference

product's documentation" [192] Accordingly, a *reference product* is defined as a biological medicinal product drug which has been used in the approval documentation of a biosimilar as the "reference for the comparability of its [the biosimilar's] pharmaceutical quality, efficacy and safety"[192] In addition, Swissmedic defines a *comparator product* as the product with which the biosimilar was compared in a comprehensive comparability exercise.[193]

Approval process: Approval of a biosimilar requires that the biosimilar is sufficiently similar to a reference product in structure, pharmaceutical quality, biologic activity, efficacy, safety, and immunogenicity to exclude relevant clinical differences with sufficient certainty.[193] The evaluation of sufficient similarity is based on a stepwise approach and the *totality of evidence*, i.e. the step-by-step evaluation of comparative analytical, functional, non-clinical, and clinical studies until biosimilarity can (or cannot) be established.[193]

With regard to choice of the comparator product for the comprehensive comparability exercise, Swissmedic requires a single comparator product to be used.[193] The Swiss reference product is recommended. Products approved in the EU or the US are also accepted, but their use must be justified as appropriate relative to the Swiss reference product if one is available.

Data requirements: In addition to analytical, chemical and pharmaceutical evaluations and comparative analytical studies of the biosimilar relative to the comparator product, clinical similarity has to be demonstrated in at least one relevant and sensitive patient population, in one indication and with one dose for which the reference product is authorised.[193] For establishing clinical similarity, clinically meaningful differences have to be excluded with sufficient statistical probability for a sufficiently sensitive indication and dose. With regard to the design of comprehensive comparative studies, Swissmedic guidance makes explicit reference to guidance from other agencies, e.g. from EMA.

Biosimilars can be submitted under Art. 13 Heilmittelgesetz (HMG, Therapeutic Products Act). This submission pathway is open if either the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA) have already approved the biosimilar.[172] [193] Swissmedic will then not conduct an independent assessment unless EMA and FDA assessments were contradictory or there was cause for concern based on EMA/FDA approval.[192] [194]

Extrapolation: In principle, a biosimilar can be approved in all indications of the reference product without document protection ("Unterlagenschutz"). Decisions about extrapolation to different indications and dosage are made on a case-by-case basis.[193] Swissmedic requires that extrapolation be scientifically justified and any associated risk for patient safety be acceptable. Biosimilarity in at least one sensitive indication and dose recommendation must have been shown for sensitive clinical or PD endpoints.

Interchangeability and provisions for automatic substitution: Automatic substitution with a biosimilar (a pharmacist dispensing a biosimilar instead of the prescribed reference product without consultation of the prescribing doctor) is not explicitly permitted in Switzerland.[172] The Swissmedic approval process does not comment on or establish whether a biosimilar is interchangeable (an interchangeable product is a biosimilar that may be substituted for the reference product without consultation of the prescriber[195]) and can be substituted for its reference product.

European Union

Key definitions: *Biosimilars* are defined as biologic medicinal products that contain a version of an active substance of an original biologic medicinal product which has been authorized in the European Economic Area (EEA). This original biologic product is referred to as the *reference (medicinal) product.*[115]

Approval process: The approval process is designed to establish similarity of the biosimilar to its reference product with regard to quality, biologic activity, safety, and efficacy in a comprehensive comparability exercise, which is called the "biosimilarity approach".[115 196] The biosimilarity approach is a stepwise approach, based on the totality of evidence.[115] It starts with physicochemical and biological assessments and evaluates any differences between the reference product and the proposed biosimilar at any stage. Differences must be explained and justified, and they inform subsequent development steps.[115 197]

The comparability exercise should be based on a single reference product, which, as per EMA guidance, must be authorised in the EEA.[115] If required, certain clinical and *in vivo* studies may use a reference product not authorised in the EEA, provided the non-EEA product has been demonstrated in a bridging study to be representative of the EEA reference product.

Data requirements: Data requirements can be derived from the steps of the biosimilarity approach. The first step are *in vitro* analytical and functional studies.[197–199] Based on first-step results, the need and suitable endpoints (PK, PD, safety) for *in vivo* and toxicity studies are assessed in the second step. The third step are clinical studies, which themselves are conducted step-by-step: First PK (and PD) studies, then (equivalence) trials on clinical efficacy and safety or confirmatory PK/PD studies.[198] This is, however, not a one-size-fits-all approach as the "nature and complexity of the reference product have an impact on the extent of the (non)clinical studies to confirm biosimilarity".[198] Clinical trials may not be required or may be waived for some products, e.g. insulins and (peg-)filgrastim.[114] (For more details on EMA data requirements, also see the recent reviews by Rathore *et al.*[200] and Rahalkar *et al.*[201]).

Extrapolation: "Extrapolation" is used to describe data for one indication, together with information on general comparability, being used to extrapolate efficacy and safety to the other indications of the reference product. Extrapolation is an established scientific and regulatory concept and not specific to biosimilars.[80]

If scientifically justified based on the totality of evidence from the comparative comparability exercise, then clinical efficacy and safety data may be extrapolated from the reference drug to the biosimilar according to EMA guidance.[198] [199] Additional data may have to be provided, e.g. if evidence on comparability is based on PD endpoints for the studied indication, but a different mode of action is relevant for the claimed indication.

Interchangeability and provisions for automatic substitution: The EMA states that there is "no reason to believe that harmful immunogenicity should be expected"[202] following a switch between highly similar biologics but does not decide on interchangeability and automatic substitution. These decisions remain with member states.[203]

United States

Key definitions: *Biosimilars* are defined as biologic products which are "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and for which there are no "clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product" (Section 351(i)(2) of the Public Health Service Act).[195] [204] The *reference product* is defined as the FDA-approved biologic against which a biosimilar is compared.[195]

Approval process: The aim of the approval process is to establish biosimilarity between the proposed biosimilar and the reference product. In particular, the two parts of the biosimilar definition must be confirmed as true: The biosimilar must be shown to be "highly similar" (mostly in *in vitro* studies) and to have no "clinically meaningful differences" (in PK, PD, immunogenicity and clinical studies).

As in the EMA biosimilarity approach, the FDA approach considers the totality of evidence and does so in a stepwise fashion.[195] [205] Comparative structural and functional characterisations should be conducted first, followed by toxicity studies, then by comparative PK and PD as well as immunogenicity studies. Additional clinical data may be required if residual uncertainty about biosimilarity remains after these steps.[195] [205]

The comparability exercise should be based on an FDA-approved reference product, in particular for analytical studies and at least one PK study (and one PD study, if applicable). However, as in the EMA's approach, a comparator from another setting can be used if bridging studies have demonstrated its comparability with the US-approved product and if the use of a non-US product is scientifically justified.[205]

The US approach is unique in that it explicitly regulates interchangeability. For a product to be designated as interchangeable, it must be shown that the biosimilar "produce[s] the same clinical result as the reference product in any given patient" and that, if the biosimilar would be administered more than once to an individual, "the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch"[206].

Data requirements: Data requirements can be derived from the approval process. Establishing biosimilarity requires structural analyses and functional assays, possibly toxicity results from animal data, pharmacologic data, immunogenicity assessments and comparative clinical studies (using equivalence designs).[205 207] However, data requirements are reviewed and adapted on a case-by-case basis.

Extrapolation: Extrapolation to additional indications is permissible if scientifically justified.[205] Justifications should be framed within the totality of evidence and should cover, among others, modes of action, PK and possibly PD measures and immunogenicity. Extrapolation is permissible only to indications also covered by the reference product.

Interchangeability and provisions for automatic substitution: Automatic substitution is possible for interchangeable products (at the time of writing, no product had yet been designated as interchangeable).[195]

For information on other countries, please see Section 12.7.

8.2.7.2 Biosimilar pricing and reimbursement in selected countries

Switzerland

Inclusion in the SL requires a drug to be efficient ("wirtschaftlich"), in addition to being effective ("wirksam") and appropriate ("zweckmässig"). In Switzerland, biosimilars are considered as efficient if, at the time of inclusion in the SL, their ex-factory price is at least 25% lower than that of the reference product.[2]

Every three years, the FOPH verifies that drugs still meet these criteria. Biosimilars are considered to meet the efficiency criteria if their ex-factory prices are at least 10% lower than average ex-factory prices of their reference products, on December 1 of the year in which verification is conducted.[2]

Inclusion in the SL implies reimbursement by mandatory healthcare insurance. Some drugs included in the SL are subject to further restrictions. In the case of infliximab (both reference product and biosimilars), prior approval from the healthcare insurance's medical officer is required.[91]

Austria

Inclusion in the Austrian Erstattungskodex (EKO; reimbursement index) requires drugs to pass a health economic evaluation.[208] For biosimilars, health economic criteria were changed in 2017 (and will in remain in force until the end of 2021). These criteria specify that when a biosimilar becomes available:[209]

- The price of the reference product must be reduced by 30% for the reference product to remain included in the EKO
- The price of the first biosimilar must be 11.4% lower than the newly reduced price of the reference product for the biosimilar to be included in the EKO
- Subsequent biosimilars are included in the EKO if the price of the second biosimilar is 15% lower than the price of the first biosimilar and the price of the third biosimilar is 10% lower than the price of the second biosimilar. If a third price reduction occurs, prices of the reference product and of the first and second biosimilar must be reduced to the price of third biosimilar for the reference product and earlier biosimilars to remain included in the EKO
- For certain indications, different arrangements can be made to promote biosimilar availability

The 2020 EKO includes four infliximab biosimilars, all classified within the "yellow box" that requires approval by a healthcare insurance medical officer.[210] The reference product (Remicade®) was excluded from the EKO in June 2018.[211]

France

Drug prices in France are set based on the drugs' improvement to medical benefit. Biosimilars are by default assessed to bring "no improvement" (ASMR V) so their price must be lower than that of the reference product.[185] The expressed (long-term) aim of the government is the removal of the price advantage of the reference product and the convergence of reference product and biosimilar prices.[212] Initial prices of biosimilars tend to be around 15-20% lower than those of their reference products, and current pricing policies agreed between state and pharmaceutical industry include initial discount rates for reference product and biosimilars of 30% in hospitals and 20% to 40% in outpatient settings.[185 212] In addition, "discount calendars" are specified to achieve price convergence in both hospitals and outpatient settings.

Germany

In Germany, drugs with no additional benefit relative to their comparator are grouped in the same reference price group ("Festbetragsgruppe") as the comparator. The reference price group determines the maximal price reimbursed by mandatory healthcare insurance for a drug from this group. Infliximab biosimilars have so far been grouped in a substance-specific reference price group as "Infliximab/Level 1" (where "Level 1" indicates that the included drugs share the same active ingredient).[213] Currently, the Federal Joint Committee are in the process of setting up a "TNF-alpha inhibitor/Level 2" reference price

group, which would include adalimumab, etanercept, golimumab, and certolizumab pegol based on their pharmacological and therapeutic comparability (which defines a Level 2 reference price group).[214]

Mandatory healthcare insurance will reimburse up to the maximum price specified by the reference price group.

Netherlands

In the Netherlands, biosimilars are not subject to specific price setting with regard to public list prices, but, like for reference products, maximum wholesale prices are determined via external reference pricing.[215] However, as determined in a study on TNF-alpha inhibitors by the Dutch Competition Agency, there is little competition based on list prices, which was attributed to an interest in keeping list prices high for external reference pricing in other countries and to retain the ability to offer substantial, frequently conditional, rebates to hospital buying groups.[187]

There is, however, competition when it comes to rebates. These rebates also apply to TNF-alpha inhibitors, which, in the Netherlands, are intramural drugs, i.e. prescribed in and (initially) paid for by hospitals even if administered at home. Rebates can be substantial, with a particularly high-profile case discussed in the Dutch press, where the manufacturer of the reference product offered a 89% conditional discount on its product after the introduction of biosimilars to the market.[216]

Hospitals are reimbursed for drug expenses by healthcare insurers on the basis of the official reference price. While some healthcare insurers reimburse a per-active ingredient reference price, others reimburse a per-cluster (of comparable medicines) reference price, thereby setting different incentives for hospitals.[187]

Norway

Norway has one of the highest biosimilar use rates globally.[217] [218] Its national medicines agency takes an explicitly pro-switch stance, stating that switching from reference product to biosimilar, vice versa and from biosimilar to biosimilar was safe, that further switching studies were unnecessary, and that switching is a necessary tool to achieve drug competition.[219] Indeed, the Norwegian state financed the largest switching study to date (NOR-SWITCH).[7]

With regard to pricing and reimbursement of biosimilars for TNF-alpha-inhibitors and infliximab, the main focus is on national tenders. Prices are negotiated by the Norwegian Drug Procurement Cooperation on behalf of state-funded hospitals that pay for treatment in the hospital and outpatient settings and for hospital prescriptions.[217] Prices are set in tenders (which, for infliximab, have included biosimilars since 2014) that rank products on two-year costs based on information submitted by manufacturers and recommendations are issued on which drug to prescribe though all available products are reimbursed.[217] [220]

9 Feasibility of an HTA

We assessed the feasibility of an HTA by availability of evidence by HTA key question/outcome and PICO (Section 6). An overview is provided in Table 14.

Table 14 Feasibility matrix for HTA key questions

	PICO 1: Infliximab-naïve	PICO 2: Switch to biosimilar	PICO 3: Switch to reference product
Clinical efficacy	Can be answered	Can be answered	Cannot be answered
Effectiveness	Can be answered	Can be answered	Cannot be answered
Safety	Can be answered	Can be answered	Cannot be answered
Health economics	Can be answered (in BIA and CEA)	Can be answered (in BIA and CEA)	Can be answered in BIA Cannot be answered in CEA
ELSO	Can be answered	Can be answered	Cannot be answered
PK/PD	Can be answered	Can be answered	Cannot be answered
Immunogenicity	Can be answered	Can be answered	Cannot be answered
PROM	Can be answered	Can be answered	Cannot be answered
Therapy discontinuation	Can be answered	Can be answered	Cannot be answered
Regulation and reimbursement	Can be answered (PICO criteria are not really applicable here)		

Abbreviations: BIA, Budget Impact Analysis; CEA, Cost-Effectiveness Analysis; ELSO, Ethical, Legal, Social, Organisational; HTA, Health Technology Assessment; PROM, Patient-Reported Outcome Measures; PD, Pharmacodynamics; PICO, Patient, Intervention, Comparator, Outcomes; PK, Pharmacokinetics.
Note: We don't mean to imply by "can be answered" that a question can be fully and definitively answered (which is rare in science). Instead, we understand this to mean that an answer can be given based on the currently available evidence.

9.1 Specific questions based on central research questions

(Clinical) Efficacy: Sufficient evidence was identified to inform an answer on efficacy of infliximab biosimilars, both in infliximab-naïve patients (PICO 1) and patients switched from the infliximab reference product (PICO 2). Evidence was available on efficacy measures of immediate clinical relevance (e.g. DAS28 and CDAI) and on efficacy measures more relevant for clinical trials (such as ACR20, ACR50, and ACR70). There was insufficient evidence to inform an answer on efficacy for patients switching from the biosimilar to the reference product.

Effectiveness: Sufficient evidence was identified to inform an answer on effectiveness of infliximab biosimilars, both in infliximab-naïve patients (PICO 1) and patients switched from the infliximab reference product (PICO 2). Notably, the studies identified for RA and infliximab for this scoping review were heterogeneous in their design and frequently small. There was insufficient evidence to inform an answer on effectiveness for patients switching from the biosimilar to the reference product.

Safety: Sufficient evidence was identified to inform an answer on safety of infliximab biosimilars, both in infliximab-naïve patients (PICO 1) and patients switched from the infliximab reference product (PICO 2). Evidence on safety was available from RCTs and from RWE studies.

Health economics: No health economic evidence was identified that would allow to answer health economic questions, on either cost-effectiveness or budget impact of the infliximab reference product relative to infliximab biosimilar in the treatment of RA, for Switzerland directly. However, sufficient evidence was available to inform modelling for Switzerland. More precisely, a BIA could be conducted for all three PICOs, which would account for different populations and include different scenarios depending on PICO. A CEA could be conducted for PICO 1 and PICO 2 (as clinical data to inform CEA modelling are available for these PICOs). The absence of evidence precluded a CEA for PICO 3.

ELSO issues: With the exception of social issues (for which no evidence was identified), sufficient evidence was identified to inform answers to questions in these domains. Answers, which cannot be definitive but can help explore important issues, could be provided for PICO 1 and PICO 2. For PICO 3, there was insufficient evidence available.

9.2 Additional outcomes of interest and additional questions

PK/PD/Immunogenicity: Sufficient evidence was identified to inform an answer on PK, PD, and immunogenic profiles, both in infliximab-naïve patients (PICO 1) and patients switched from the infliximab reference product (PICO 2). Evidence on these profiles was available predominantly from RCTs although RWE studies also provided information on these issues. For PICO 3, evidence was insufficient.

PROMs: Sufficient evidence was identified to inform an answer on PROMs associated with infliximab biosimilars, both in infliximab-naïve patients (PICO 1) and patients switched from the infliximab reference product (PICO 2). Evidence on PROMs was available predominantly from RCTs although RWE studies also provide some information on these issues. Key PROMs reported include functional status, patient global assessment, and HRQoL. For PICO 3, there was insufficient evidence available.

Therapy discontinuation: Sufficient evidence was available to inform an answer on treatment discontinuation associated with infliximab biosimilars, both in infliximab-naïve patients (PICO 1) and patients switched from the infliximab reference product (PICO 2). Notably, evidence on treatment discontinuation was available from both RCTs and RWE studies. Both types of studies explored reasons for discontinuation, e.g. AEs. However, RWE studies also explored non-medical reasons for discontinuation, which could help assess the role of nocebo effects.

Regulation and reimbursement: Different regulation and reimbursement procedures could be reviewed and summarised.

9.3 Suggested changes to PICO

In light of the absence of evidence on PICO 3, it may be worth removing PICO 3 for a full HTA. Given the currently relatively low uptake of infliximab biosimilars in Switzerland, this PICO may also be of little relevance to clinical and regulatory practice.

10 Outlook

After commenting on the feasibility of a full HTA in the previous section (Section 9), we discuss approaches to synthesise evidence on efficacy and effectiveness and to obtain Swiss-specific health economic assessments.

10.1 Synthesising evidence on clinical efficacy and safety

Existing reviews of efficacy and safety: For synthesising efficacy and effectiveness evidence, we base our discussion, in part, on existing systematic reviews of biosimilars in general and infliximab in particular (Appendix table 8 and Appendix table 9). Note that, at the request of the FOPH, we focussed our literature searches on primary studies. However, to cross-check our search results and assess our findings in context, we conducted a non-systematic search for existing reviews of biosimilars for infliximab (and TNF-alpha inhibitors more broadly) that included RA. We do not claim that this search was exhaustive, but we are confident to have identified relevant reviews that can help provide context for this section.

Existing reviews have shown that the evidence on efficacy and safety of biosimilars, including those of infliximab, in RA for treatment-naïve and switched patients consistently indicated similar efficacy, safety, and immunogenicity between reference products and biosimilars although evidence gaps remain with regard to switching (Appendix table 8). Some existing reviews of biosimilars of TNF-alpha inhibitors in general and infliximab in particular also performed meta-analyses on comparative efficacy and safety.[221–223] These reviews used ACR response criteria as their main efficacy outcome and (serious) AEs as their main safety outcome. Again, their results consistently showed similar efficacy and safety between reference products and biosimilars.

Existing reviews have considered most RCTs of biosimilars to be of good to very good quality and to have been reported according to guidelines.[131 223–225] This also applied to RCTs of infliximab biosimilars, which were included in both existing reviews and this scoping report (Appendix table 9). Trial populations and designs were similar across RCTs, and all but one RCT were conducted in samples of more than 100 patients (Table 8). These findings indicate that a quantitative synthesis of RCT results would likely be feasible and based on solid evidence.

However, it would need to be kept in mind that any synthesis would be conducted separately for each PICO and outcome domain, which would reduce the number of trials and patients available for PICO 2 in particular (as studies on the initial, non-switch phases of many RCTs would not inform the synthesis for this PICO). As pointed out by Numan and Faccin[130] and Feagan *et al.*[131], few of the RCTs that investigated switching to infliximab biosimilar were powered to detect post-switch efficacy differences, and

some did not have a control group but were continued as single-arm extension studies of initial RCTs. In addition, there are, to date, no studies investigating multiple switching for infliximab.

Outlook for a full HTA: We would suggest to conduct a *de novo* synthesis of RCTs in a full HTA. This would allow to obtain a synthesis that is tailored to inform the decision problem at hand using inclusion/exclusion criteria approved by the FOPH and that incorporates the most recent evidence, including recent studies that were not available to existing systematic reviews (Appendix table 9).

Based on the results of this scoping report and on existing reviews, we would suggest to perform:

- Quantitative synthesis, i.e. a meta-analysis, separately for clinical efficacy, safety, immunogenicity, and PROM results, which were frequently reported by RCTs. We anticipate that meta-analyses can be conducted for both PICO 1 and PICO 2 but that the synthesis for PICO 2 will likely be limited in the strength of its conclusions due to the aforementioned caveats. Endpoints would be chosen in discussion with the FOPH and reviewers, and they would likely include ACR criteria for efficacy, AE rates for safety, ADAb rates for immunogenicity, and functional status for PROMs.

  Depending on the number and timing of endpoints to be considered, standard meta-analysis may be insufficient and more advanced methods may be required, e.g. multivariate meta-analysis to account for correlation of outcomes among each other and over time, subject to data availability.[226–230]
- Synthesis without meta-analysis for PK/PD outcomes, which were less frequently reported, and for those efficacy, safety, immunogenicity, and PROM outcomes that were not included in the respective meta-analysis.[231] This type of synthesis was used frequently in existing reviews of biosimilars.[131 232 233]

10.2 Synthesising evidence on real-world effectiveness and safety

Existing reviews of effectiveness and safety: Most of the existing reviews of biosimilar included RWE studies, either exclusively or in addition to RCTs (Appendix table 8 and Appendix table 9).[100 147 232–234] Few of these reviews formally assessed the quality of RWE studies. Where such an assessment was performed, the primary studies were considered to be of fair quality although a 2018 review stated that none of its included RWE studies (many of which we identified for the scoping report, see Appendix table 9) met the requirements for a robust switching study.[130 235] The RWE studies identified for the scoping report differed substantially in their study designs and were frequently based on small sample sizes, with only few studies reporting on any one outcome. Still, RWE studies remain an indispensable source of information, for therapy discontinuation and nocebo effects in particular. Notably, as pointed

out by Kilcher *et al.* (2018) differences in patient populations between RCTs and observational studies may imply that efficacy estimates generated in RCTs differ from effectiveness estimates generated in RWE studies.[236] This provides another rationale for considering RWE in the HTA.

Outlook for a full HTA: We would suggest to synthesise real-world evidence, including evidence on effectiveness, safety, immunogenicity, PROMs, and treatment discontinuation (including nocebo effects), narratively but without a meta-analysis, e.g. in a format similar to Bakalos and Zintzaras[235] and Odinet *et al.*[147]. This would be in line with the existing literature and would allow us to explore outcomes in detail.

10.3 Generating health economic evidence

Health economic evaluations for biosimilars, which we identified for the scoping report, were BIAs, in addition to costing studies (Table 12). The use of BIAs and of cost-minimisation analysis is generally considered to be appropriate to inform biosimilar reimbursement if a reference product is available as standard of care (as would be the case with infliximab in Switzerland).[237–239] In contrast, a full economic evaluation might be required only if no reference product is reimbursed and if there are concerns about nocebo effects and differences in therapy discontinuation.[239] There is, however, little guidance available on which type of full economic evaluation would be required in such a case and how, for example, to account for clinically irrelevant differences between reference products and biosimilars in long-term modelling.

In line with the evidence base identified for the scoping report and the literature, we would suggest to focus on budget impact and possibly cost-minimisation analysis in a full HTA. Recent work for Switzerland by Kobler *et al.*[158] could possibly be adapted or extended. Key data requirements for any BIA would include epidemiologic, resource use, and market share data, including precise data on the number of individuals treated with infliximab for RA, which might prove challenging to calculate even with access to high-quality Swiss data sources such as health insurance claims data or the Swiss Clinical Quality Management Register.

Based on available evidence, we do not think that a full economic evaluation will be required or an efficient use of resources. However, if a need for a full economic evaluation were to be perceived, existing models for assessment of treatment sequences in RA could be used. Examples include Markov cohort models but also individual patient simulation models.[160 161 240] Of particular interest, in our view, might be the open-source IVI-RA model, an individual patient simulation model that could be adapted from the US to the Swiss setting.[241 242] Still, we do not currently anticipate a need for a full economic evaluation.

In a full HTA, all literature searches conducted for the scoping review would be re-run and updated. In addition, the literature would be assessed for quality and overall certainty, with standard tools for assessment of bias and for rating certainty of evidence.[243–246]

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12 Appendices

12.1 Search strategies for efficacy, safety, effectiveness and health economic searches

Appendix table 1 Search strategy for the Cochrane Library

Step	Item	Search string	Hits
#1	Disease (population)	(((rheumatoid OR reumatoid OR revmatoid OR rheumatic OR reumatic OR revmatic OR rheumat* OR reumat* OR revmarthrit*) NEAR/3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)) OR rheumatolog*):ti,ab,kw	21,396
#2	Intervention and health economics	(infliximab OR remicade OR cost* OR economic* OR budget* OR "pharmaco-economic*" OR expenditure* OR pric* OR priz* OR financ* OR value* OR mone* OR markov* OR "monte carlo" OR "decision tree*" OR “microsimulation” OR “discrete event simulation”):ti,ab,kw	241,773
#3	Comparator	((remsima OR inflectra OR "ABP 710" OR ABP710 OR flammegis OR "CT-P13" OR ixifi OR "PF-06438179" OR PF6438179 OR PF06438179 OR infimab OR "STI-002" OR "NI-071" OR "infliximab BS" OR BOW015 OR flixabi OR renflexis OR zessly OR baimaibo OR gp1111 OR "gp 1111" OR revellex OR avsola OR sb2 OR "gp-2018" OR bcd055 OR "rtpr-015" OR biosimilar* OR biogeneric* OR (("follow-on" OR "subsequent-entry" OR "me-too" OR "non-innovator") NEAR/3 biologic*))):ti,ab,kw	1,041
#4	Combine	#1 AND #2 AND #3	155

Appendix table 2 Search strategy (1 of 2) for Medline (via EBSCOhost)

Step	Item	Search string	Hits
#1	Disease (population)	((MH "Arthritis, Rheumatoid+") OR (MH "Rheumatology")) OR TI (((rheumatoid OR reumatoid OR revmatoid OR rheumatic OR reumatic OR revmatic OR rheumat* OR reumat* OR revmarthrit*) N3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)) OR rheumatolog*) OR AB (((rheumatoid OR reumatoid OR revmatoid OR rheumatic OR reumatic OR revmatic OR rheumat* OR reumat* OR revmarthrit*) N3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)) OR rheumatolog*)	182,967
#2	Intervention and health economics	((MH "Infliximab") OR (MH "Economics+")) OR TI (infliximab OR remicade OR cost* OR economic* OR budget* OR "pharmaco-economic*" OR expenditure* OR pric* OR priz* OR financ* OR value* OR mone* OR markov* OR "monte carlo" OR "decision tree*" OR “microsimulation” OR “discrete event simulation”) OR AB (infliximab OR remicade OR cost* OR economic* OR budget* OR "pharmaco-economic*" OR expenditure* OR financ* OR value* OR mone* OR markov* OR "monte carlo" OR "decision tree*")	3,118,573
#3	Comparator	(MH "Biosimilar Pharmaceuticals") OR TI ((remsima OR inflectra OR "ABP 710" OR ABP710 OR flammegis OR "CT-P13" OR ixifi OR "PF-06438179" OR PF6438179 OR PF06438179 OR infimab OR "STI-002" OR "NI-071" OR "infliximab BS" OR BOW015 OR flixabi OR renflexis OR zessly OR baimaibo OR gp1111 OR "gp 1111" OR revellex OR avsola OR sb2 OR "gp-2018" OR bcd055 OR "rtpr-015" OR biosimilar* OR biogeneric* OR (("followon" OR "subsequent entry" OR "me-too" OR "non-innovator") N3 biologic*))) OR AB ((remsima OR inflectra OR "ABP 710" OR ABP710 OR flammegis OR "CT-P13" OR ixifi OR "PF-06438179" OR PF6438179 OR PF06438179 OR infimab OR "STI-002" OR "NI-071" OR "infliximab BS" OR BOW015 OR flixabi OR renflexis OR	4,478

Step	Item	Search string	Hits
		zessly OR baimaibo OR gp1111 OR "gp 1111" OR revellex OR avsola OR sb2 OR "gp-2018" OR bcd055 OR "rtpr-015" OR biosimilar* OR biogeneric* OR (("followon" OR "subsequent entry" OR "me-too" OR "non-innovator") N3 biologic*)))	
#4	Combine	#1 AND #2 AND #3	310
#5	Exclude non-human studies	S1 AND S2 AND S3 NOT ((MH "Animals") NOT (MH "Humans"))	308

Appendix table 3 Search strategy for Embase

Step	Item	Search string	Hits
#1	Disease (population)	'rheumatoid arthritis'/exp OR 'rheumatology'/exp OR (((rheumatoid OR reumatoid OR revmatoid OR rheumatic OR reumatic OR revmatic OR rheumat* OR reumat* OR revmarthrit*) NEAR/3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)):ti,ab) OR rheumatolog*:ti,ab	321,459
#2	Intervention and health economics	'infliximab'/exp OR infliximab:ti,ab OR remicade:ti,ab OR 'economics'/exp OR cost*:ti,ab OR economic*:ti,ab OR budget*:ti,ab OR 'pharmaco-economic*':ti,ab OR expenditure*:ti,ab OR pric*:ti,ab OR priz*:ti,ab OR financ*:ti,ab OR value*:ti,ab OR mone*:ti,ab OR markov*:ti,ab OR 'monte carlo':ti,ab OR 'decision tree*':ti,ab OR microsimulation:ti,ab OR 'discrete event simulation':ti,ab	3,845,217
#3	Comparator	'biosimilar agent'/exp OR remsima:ti,ab OR inflectra:ti,ab OR 'abp 710':ti,ab OR abp710:ti,ab OR flammegis:ti,ab OR 'ct-p13':ti,ab OR ixifi:ti,ab OR 'pf-06438179':ti,ab OR pf6438179:ti,ab OR pf06438179:ti,ab OR infimab:ti,ab OR 'sti-002':ti,ab OR 'ni-071':ti,ab OR 'infliximab bs':ti,ab OR bow015:ti,ab OR flixabi:ti,ab OR renflexis:ti,ab OR zessly:ti,ab OR baimaibo:ti,ab OR gp1111:ti,ab OR 'gp 1111':ti,ab OR revellex:ti,ab OR avsola:ti,ab OR sb2:ti,ab OR 'gp-2018':ti,ab OR bcd055:ti,ab OR 'rtpr-015':ti,ab OR biosimilar*:ti,ab OR biogeneric*:ti,ab OR ((('follow-on' OR 'subsequent-entry' OR 'me-too' OR 'non-innovator') NEAR/3 biologic*):ti,ab)	8,078
#4	Combine	#1 AND #2 AND #3	1,042
#5	Exclude non-human studies	#1 AND #2 AND #3 NOT ([animals]/lim NOT [humans]/lim)	1,030

Appendix table 4 Search strategy for EconLit (via EBSCOhost)

Step	Item	Search string	Hits
#1	Disease (population)	TX ((rheumatoid OR reumatoid OR revmatoid OR rheumatic OR reumatic OR revmatic OR rheumat* OR reumat* OR revmarthrit*) N3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)) OR rheumatolog*	60
#2	Intervention	TX infliximab OR remicade OR cost* OR economic* OR budget* OR "pharmacoeconomic*" OR expenditure* OR pric* OR priz* OR	1,450,783

Step	Item	Search string	Hits
	and health economics	financ* OR value* OR mone* OR markov* OR "monte carlo" OR "decision tree*" OR microsimulation OR “discrete event simulation”	
#3	Comparator	TX (remsima OR inflectra OR "ABP 710" OR ABP710 OR flammegis OR "CT-P13" OR ixifi OR "PF-06438179" OR PF6438179 OR PF06438179 OR infimab OR "STI-002" OR "NI-071" OR "infliximab BS" OR BOW015 OR flixabi OR renflexis OR zessly OR baimaibo OR gp1111 OR "gp 1111" OR revellex OR avsola OR sb2 OR "gp-2018" OR bcd055 OR "rtpr-015" OR biosimilar* OR biogeneric* OR (("followon" OR "subsequent entry" OR "me-too" OR "non-innovator") N3 biologic*))	43
#4	Combine	#1 AND (#2 OR #3)	52

Appendix table 5 Search strategy for PsycInfo (via EBSCOhost)

Step	Item	Search string	Hits
#1	Disease (population)	DE "Rheumatoid Arthritis" OR TX (((rheumatoid OR reumatoid OR revmatoid OR rheumatic OR reumatic OR revmatic OR rheumat* OR reumat* OR revmarthrit*) N3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)) OR rheumatolog*)	6,282
#2	Intervention and health economics	((DE "Economics" OR DE "Health Care Economics")) OR TX (infliximab OR remicade OR cost* OR economic* OR budget* OR "pharmaco-economic*" OR expenditure* OR pric* OR priz* OR financ* OR value* OR mone* OR markov* OR "monte carlo" OR "decision tree*" OR “microsimulation” OR “discrete event simulation”)	676,322
#3	Comparator	TX (remsima OR inflectraOR "ABP 710" OR ABP710 OR flammegis OR "CT-P13" OR ixifi OR "PF-06438179" OR PF6438179 OR PF06438179 OR infimab OR "STI-002" OR "NI-071" OR "infliximab BS" OR BOW015 OR flixabi OR renflexis OR zessly OR baimaibo OR gp1111 OR "gp 1111" OR revellex OR avsola OR sb2 OR "gp-2018" OR bcd055 OR "rtpr-015" OR biosimilar* OR biogeneric* OR (("followon" OR "subsequent entry" OR "me-too" OR "non-innovator") N3 biologic*))	112
#4	Combine	#1 AND #2 AND #3	0

12.2 Search strategies for ethical, social, legal and organizational issues

Appendix table 6 Search strategy (2 of 2) for Medline (via EBSCOhost)

Step	Item	Search string	Hits
#1	Biosimilar	(MH "Biosimilar Pharmaceuticals" OR TI ((biosimilar* OR biogeneric* OR (("followon" OR "subsequent entry" OR "me-too" OR "non-innovator") N3 biologic*))) OR AB ((biosimilar* OR biogeneric* OR (("followon" OR "subsequent entry" OR "me-too" OR "non-innovator") N3 biologic*))))	4,185
#2	Ethical, social, legal items	(MH "Ethical Analysis" OR MH "Legislation, Drug" OR MH "Social Change" OR TI ((ethic OR legal OR law OR social)) OR AB ((ethic OR legal OR law OR social)))	776,147

Step	Item	Search string	Hits
#3	Organizational items	(MH "Organization and Administration" OR MH "Policy" OR MH "Insurance, Health" OR MH "Insurance Coverage" OR MH "Drug Approval" OR MH "Health Services Accessibility" OR TI ((organization OR policy OR approval OR coverage OR regulation OR regulatory OR reimburse* OR access)) OR AB ((organization OR policy OR approval OR coverage OR regulation OR regulatory OR reimburse* OR access)))	3,509,714
#4	Countries	(MH "Switzerland" OR MH "France" OR MH "Germany" OR MH "Italy" OR MH "Spain" OR MH "United Kingdom" OR MH "England" OR MH "Scotland" OR MH "Northern Ireland" OR MH "Wales" OR MH "Belgium" OR MH "Luxemburg" OR MH "Netherlands" OR MH "Denmark" OR MH "Finland" OR MH "Norway" OR MH "Sweden" OR MH "Australia" OR MH "United States" OR MH "Canada" OR TI ((switzerland or swiss or france or french or german* or italian or spain or spanish or "united kingdom" or "britain" or british or england or scotland or "northern ireland" or wales or belgium or belgian or luxemburg or netherlands or holland or dutch or denmark or danish or finland or finnish or norway or norwegian or sweden or swedish or australia or "united states" or canada or canadian)) OR AB ((switzerland or swiss or france or french or german* or italian or spain or spanish or "united kingdom" or "britain" or british or england or scotland or "northern ireland" or wales or belgium or belgian or luxemburg or netherlands or holland or dutch or denmark or danish or finland or finnish or norway or norwegian or sweden or swedish or australia or "united states" or canada or canadian)))	2,611,312
#5	Combine	#1 AND (#2 OR (#3 AND #4))	599

12.3 List of HTA agency websites searched

Australia: Australian Government Department of Health (https://www1.health.gov.au/internet/hta/publishing.nsf/Content/home-1)
Canada: Canadian Agency for Drugs and Technologies in Health (http://www.cadth.ca)
France: Haute Autorité de Santé (http://www.has-sante.fr/)
Germany: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (https://www.iqwig.de/)
Netherlands: Zorginstituut Nederland (https://www.zorginstituutnederland.nl/)
United Kingdom: National Institute for Health and Care Excellence (https://www.nice.org.uk/)
United States: Institute for Clinical and Economic Review (https://icer-review.org/)

12.4 List of regulatory agency websites

Swissmedic (https://www.swissmedic.ch/swissmedic/de/home.html)
European Medicines Agency (https://www.ema.europa.eu/en)
Austria: Bundesamt für Sicherheit im Gesundheitswesen (https://www.basg.gv.at/)
France: Agence Nationale de Sécurite du Médicament et des Produits de Santé (https://www.ansm.sante.fr/Mediatheque/Publications/Information-in-English)
Germany: Gemeinsamer Bundesausschuss (https://www.g-ba.de/) and Paul-Ehrlich-Institut (https://www.pei.de/DE/home/home-node.html)
Italy: Agenzia Italiana del Farmaco (https://www.aifa.gov.it/)
Spain: Ministry of Health, Consumer Affairs and Social Welfare (https://www.mscbs.gob.es/en/home.htm)
United Kingdom: Medicines & Healthcare products Regulatory Agency (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency)
Belgium: Federal Agency for Medicines and Health Products (https://www.famhp.be/en)
Luxemburg: Ministry of Health (http://sante.public.lu/fr/politique-sante/ministere-sante/index.html)
Netherlands: Medicines Evaluation Board (https://www.cbg-meb.nl/)
Denmark: Danish Medicines Agency (https://www.cbg-meb.nl/)
Finland: Finnish Medicines Agency (https://www.fimea.fi/)
Norway: Norwegian Medicines Agency (https://legemiddelverket.no/English)
Sweden: National Board of Health and Welfare (https://www.socialstyrelsen.se/)
Australia: Therapeutic Goods Administration (https://www.tga.gov.au)
US: Food and Drug Administration (https://www.fda.gov/
Canada: Health Canada (https://www.canada.ca/en/health-canada.html)

12.5 Studies excluded during full text review

12.5.1 Studies excluded from searches for evidence on efficacy, safety, effectiveness and health economic outcomes

1 Abdalla A, Byrne N, Conway R, *et al.* Long-term safety and efficacy of biosimilar infliximab among patients with inflammatory arthritis switched from reference product. Open Access Rheumatol 2017;9:29–35. 10.2147/OARRR.S124975 *not target country*

2 Aladul MI, Fitzpatrick RW, Chapman SR. Patients' understanding and attitudes towards infliximab and etanercept biosimilars: result of a UK web-based survey. BioDrugs 2017;31:439–46. 10.1007/s40259-017-0238-1 *not target outcome*

3 Alghamdi A, Alduraibi D. Utilizations and expenditures of tumor necrosis factor antagonists in Medicare Part D: cross- sectional study (2014-2015). Value Health 2018;21:S167. 10.1016/j.jval.2018.09.994 *not target publication status*

4 Ali SS, Hill D, Sofat N. Audit examining the difference in clinical outcomes amongst originator biologic treated patients with RA, PSA and AXSPA who were switched to biosimilar versions and monitored routinely at st george's university hospital nhs trust. Rheumatology 2019;58:iii121–2. 10.1093/rheumatology/kez107.012 *not target publication status*

5 Bansback N, Curtis JR, Huang J, *et al.* Patterns of biosimilar use in the rheumatology informatics system for effectiveness (RISE) registry. Arthritis and Rheumatology 2018;70:2110–1. 10.1002/art.40700 *not target outcome*

6 Barbieri M, Wong JB, Drummond M. The Cost Effectiveness of Infliximab for Severe Treatment-Resistant Rheumatoid Arthritis in the UK. PharmacoEconomics 2005;23:607–18. *not target comparator*

7 Bocquet F., Fusier I., Cordonnier A., *et al.* Budget impact analysis of implementing tenders between the branded infliximab and its biosimilars in the public hospitals of Paris. Value Health 2015;18:A639. *not target publication status*

8 Bocquet F., Fusier I., Cordonnier A., *et al.* Biosimilar infliximab in the 37 public hospitals of Paris: Meeting the challenge of substitution. Value Health 2016;19:A445. *not target publication status*

9 Bocquet F., Fusier I., Cordonnier A.L., *et al.* Marketing of the first biosimilar infliximab in France: What budgetary impact in the public hospitals of Paris? Fundam Clin Pharmacol 2016;30:80. 10.1111/fcp.12190 *not target publication status*

10 Borras Blasco J, Gracia-Pérez A, Casterá D, *et al.* Clinical and economic impact of the use of infliximab biosimilar inflectra in rheumatoid arthritis, psoriatic arthropathy and ankylosing spondylitis patients. Value Health 2016;19:A546. *not target publication status*

11 Braun J, Baraliakos X, Kudrin A, *et al.* … (ADA) in Patients with Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) in Response to Infliximab (INF) and Its Biosimilar CT-P13.: L21. Arthritis & Rheumatology 2014. *not target publication status*

12 Braun J, Park W, Yoo DH, *et al.* FRI0119 What Intrinsic and Extrinsic Factors Affect the Developement of Anti-Drug Antibody to Innovator Infliximab and its Biosimilar CT-P13 in Rheumatoid Arthritis and Ankylosing Spondylitis. Ann Rheum Dis 2015;74:463–4. 10.1136/annrheumdis-2015-eular.4406 *not target publication status*

13 Chanroux L., Mboge F., Wadiwalla A. HPR biosimilar use among European rheumatoid arthritis patients and impact on patient outcomes. Ann Rheum Dis 2017;76:1505. 10.1136/annrheumdis-2017-eular.6598 *not target publication status*

14 Choe J-Y, Smolen J, Keystone E, *et al.* Efficacy and safety analysis by overall anti-drug antibody result up to week 30 in patients with rheumatoid arthritis treated with SB2 (an infliximab biosimilar) or reference infliximab in a phase III study. J Rheumatol 2017;44:872. 10.3899/jrheum.170256 *not target publication status*

15 Chopra A, Chopra I, Giardina C, *et al.* Shift in the status QUO: How biosimilar interchangeability can lead to significant cost savings. Value Health 2018;21:S101. *not target publication status*

16 Codreanu C, Sirova K, ... … and Safety of CT-P13 (Biosimilar Reference Infliximab) in a Real-Life Setting in 151 Patients with Rheumatoid Arthritis and Ankylosing Spondylitis: A Mid …. ARTHRITIS & … 2016. *not target publication status*

17 Cohen S, Alten R, Kameda H, *et al.* … comparing PF-06438179/GP1111 (an infliximab biosimilar) and infliximab reference product for treatment of moderate to severe active rheumatoid arthritis …. Arthritis … Published Online First: 2018.https://arthritis-research.biomedcentral.com/articles/10.1186/s13075-018-1646-4. *duplicate*

18 Convertino I, Tuccori M, Lucenteforte E, *et al.* Switching from infliximab-originator to infliximab-biosimilar in rheumatologic patients: The clinical impact in Tuscan Region, Italy. Pharmacoepidemiol Drug Saf 2019;28:477–8. 10.1002/pds.4864 *not target publication status*

19 Cutroneo PM, Isgrò V, Russo A, *et al.* Safety profile of biological medicines as compared with non-biologicals: an analysis of the Italian spontaneous reporting system database. Drug Saf 2014;37:961–70. 10.1007/s40264-014-0224-1 *not target intervention*, *not target comparator*

20 Di Giuseppe D, Frisell T, Ernestam S, *et al.* Uptake of rheumatology biosimilars in the absence of forced switching. Expert Opin Biol Ther 2018;18:499–504. 10.1080/14712598.2018.1458089 *not target outcome*

21 Emery P, Weinblatt ME, Smolen JS, *et al.* Impact of immunogenicity on clinical efficacy and administration related reaction in TNF inhibitors: A pooled-analysis from three biosimilar studies in patients with rheumatoid arthritis. Arthritis Rheum 2018;70:1694–5. 10.1002/art.40700 *not target publication status*

22 Emond B, Ellis L, Pires A, *et al.* Treatment and switching patterns in patients with immune-mediated inflammatory diseases treated with originator infliximab or its biosimilars. J Manag Care Spec Pharm 2019;25:S82. *not target publication status*

23 Ewara EM, Ellis L, Goyal K, *et al.* A comparative real-world utilization patterns of innovator and biosimilar infliximab in a treatment naïve and switch population from Germany: A prescription claims analysis. Ann Rheum Dis 2018;77:965. 10.1136/annrheumdis-2018-eular.1327 *not target publication status*

24 Fernández CG, Peña CG, Romero RM, *et al.* Experience of biosimilar infliximab in daily practice in a third level hospital. Int J Clin Pharm 2018;40:209. 10.1007/s11096-017-0565-9 *not target publication status*

25 Flemming P. The anti-TNF biosimilar CT-P13 had equivalent efficacy to infliximab in rheumatoid arthritis over one year. GaBI J 2016;5:96–96. 10.5639/gabij.2016.0502.024 *not target study design*

26 Franco CP, De La Rubia Nieto A. Evolution of costs in biological intravenous treatments in rheumatic diseases over 5 years. Euro J Hosp Pharm Sci Pra 2017;24:A220. 10.1136/ejhpharm-2017-000640.490 *not target publication status*

27 Frantzen L, Cohen J-D, Tropé S, *et al.* Patients' concerns about and perception of biosimilars in rheumatology : A French survey. Ann Rheum Dis 2018;77:608. 10.1136/annrheumdis-2018-eular.4888 *not target publication status*

28 Frantzen L, Cohen J-D, Tropé S, *et al.* Patients' information and perspectives on biosimilars in rheumatology: a French nation-wide survey. Joint Bone Spine 2019;86:491–6. 10.1016/j.jbspin.2019.01.001 *not target publication status*

29 García MC, Bargiela NF, Queiruga MG, *et al.* Cost of treatment analysis of biosimilar and innovator infliximab in a tertiary level hospital. Euro J Hosp Pharm Sci Pra 2017;24:A179–80. 10.1136/ejhpharm-2017-000640.396 *not target publication status*

30 García-Fernandez C, Ruiz-Fuentes S, Belda-Rustarazo S, *et al.* Economic impact of biosimilar infliximab use. Euro J Hosp Pharm Sci Pra 2018;25:A15. 10.1136/ejhpharm-2018-eahpconf.34 *not target publication status*

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66 Nurmohamed M, Bos R, Kok M, *et al.* No clinical relevant changes in efficacy, quality of life and tolerability for RA patients in clinical remission 16 weeks after switching to the biosimilar IFX CT-P13 compared to the originator; a descriptive report. Ann Rheum Dis 2019;78:1658. 10.1136/annrheumdis-2019-eular.7286 *not target publication status*

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84 Shah A, Mwamburi M. Modeling the budget impact of availability of biosimilars of infliximab and adalimumab for treatment for rheumatoid arthritis using published claim-based algorithm data in the United States. Value Health 2016;19:A228. *not target publication status*

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86 Smolen JS, Choe J-Y, Weinblatt ME, *et al.* Pooled analysis of TNF inhibitor biosimilar studies comparing radiographic progression by disease activity states in rheumatoid arthritis. RMD Open 2020;6. 10.1136/rmdopen-2019-001096 *not target publication status*

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88 Teeple A, Ginsburg S., Howard L., *et al.* Patient attitudes about non-medical switching to biosimilars: results from an online patient survey in the United States. Curr Med Res Opin 2019;35:603–9. 10.1080/03007995.2018.1560221 *not target intervention*, *not target comparator*

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90 Valido A, Silva-Dinis J, Saavedra MJ, *et al.* Efficacy and cost analysis of a systematic switch from originator infliximab to biossimilar CT-P13 of all patients with inflammatory arthritis from a single centre. Ann Rheum Dis 2018;77:1712–3. 10.1136/annrheumdis-2018-eular.5844 *not target publication status*

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96 Yoo D, Miranda P, Piotrowski M, *et al.* FRI0143 A randomized, double-blind, phase 3 study demonstrates clinical equivalence of CT-P13 to infliximab when co-administered with methotrexate in patients with active rheumatoid arthritis. Annals of the Rheumatic Diseases 2013;71:359–359. 10.1136/annrheumdis-2012-eular.2600 *not target publication status*

97 Yoo D, Park W, Miranda P, *et al.* Inhibition of radiographic progression and its association with clinical parameters in RA patients treated with CT-P13 and innovator infliximab in planetra study. Ann Rheum Dis 2014;73. 10.1136/annrheumdis-2014-eular.3056 *not target publication status*

98 Yoo D-H, Park W, Brzosko M, *et al.* Disease activity assessment using the DAS28, CDAI and SDAI and effect of anti-drug antibody on clinical response in a randomized, double-blind, comparative trial of CT-P13 and innovator infliximab: Planetra study. Ann Rheum Dis 2014;73. 10.1136/annrheumdis-2014-eular.3707 *not target publication status*

99 Yoo DH, Park W, Shim SC, *et al.* Infliximab is effective in the treatment of rheumatoid arthritis regardless of body mass index: Post-hoc analysis of PLANETRA. Int J Rheum Dis 2017;20:125. 10.1111/1756-185X.13178 *not target publication status*

100 Yoo DH, Shevchuk S., Ramiterre E., *et al.* Local tuberculosis incidence affects the rate of positive conversion in the quantiferon®-TB gold test among patients receiving infliximab or CT-p13 therapy. Ann Rheum Dis 2013;72. 10.1136/annrheumdis-2013-eular.1291 *not target publication status*

12.5.2 Studies excluded from searches for evidence on ELSO outcome searches

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2 Azevedo V, Hassett B, Fonseca JE, *et al.* Differentiating biosimilarity and comparability in biotherapeutics. Clin Rheumatol 2016;35:2877–86. 10.1007/s10067-016-3427-2 *not target outcome*

3 Barbosa MDFS. Immunogenicity of biotherapeutics in the context of developing biosimilars and biobetters. Drug Discov Today 2011;16:345–53. 10.1016/j.drudis.2011.01.011 *not target outcome*

4 Casadevall N, Edwards IR, Felix T, *et al.* Pharmacovigilance and biosimilars: considerations, needs and challenges. Expert Opin Biol Ther 2013;13:1039–47. 10.1517/14712598.2013.783560 *not target outcome*

5 Chang L-C. The biosimilar pathway in the USA: an analysis of the innovator company and biosimilar company perspectives and beyond. Journal of Food and Drug Analysis 2019;27:671–8. 10.1016/j.jfda.2019.03.003 *not target outcome*

6 Chen B, Nagai S, Armitage JO, *et al.* Regulatory and clinical experiences with biosimilar filgrastim in the U.S., the European Union, Japan, and Canada. Oncologist 2019;24:537–48. 10.1634/theoncologist.2018-0341 *not target outcome*

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8 College ter Beoordeling van Geneesmiddelen. Originele biologische medicijnen en biosimilars. 2018. [cited 2020 21 February] https://www.cbg-meb.nl/onderwerpen/medicijninformatie-originele-biologische-medicijnen-en-biosimilars. *not target outcome*

9 Endrenyi L, Chang C, Chow S-C, *et al.* On the interchangeability of biologic drug products. Stat Med 2013;32:434–41. 10.1002/sim.5569 *not target outcome*

10 Epstein MS, Ehrenpreis ED, Kulkarni PM, *et al.* Biosimilars: the need, the challenge, the future: the FDA perspective. Am J Gastroenterol 2014;109:1856–9. 10.1038/ajg.2014.151 *not target publication status*

11 Furlanetto A, Purcell N. Biologics and biosimilars: a legal perspective from Canada. Pharmaceutical Patent Analyst 2016;5:79–81. 10.4155/ppa-2016-0001 *not target publication status*

12 Gavrilă R, Isailă M, Mircioiu C, *et al.* Biostatistic, legislativ and ethical problems of comparative clinical studies. i. generic and biosimilar drugs case. … Published Online First: 2018.http://www.revistafarmacia.ro/201806/2018-06-art-02-Gavrila_Prasacu_Mircioiu_930-937.pdf. *not target publication status*

13 Karalis V, Macheras P. Current regulatory approaches of bioequivalence testing. Expert Opin Drug Metab Toxicol 2012;8:929–42. 10.1517/17425255.2012.690394 *not target publication status*

14 Kingham RF, Lietzan E. Current regulatory and legal considerations for follow-on biologics. Clin Pharmacol Ther 2008;84:633–5. 10.1038/clpt.2008.159 *not target publication status*

15 Klijn SL, Reek JMPA van den, Wetering G van de, *et al.* Biologic treatment sequences for plaque psoriasis: a cost–utility analysis based on 10 years of Dutch real-world evidence from BioCAPTURE. Br J Dermatol 2018;178:1181–9. 10.1111/bjd.16247 *not target outcome*

16 Lietzan E. Biosimilar law and regulation: an essential guide. FDLI Monograph Series Published Online First: 2011.https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2220857. *not target publication status*

17 Looper YJ. Legislative initiatives in Europe, Canada and the US for market authorization of follow-on biologics. Current Opinion In Drug Discovery & Development 2010;13:247–56. *not target publication status*

18 Martin LF. The biopsychosocial characteristics of people seeking treatment for obesity. Obes Surg 1999;9:235–43. 10.1381/096089299765553098 *not target intervention, not target comparator, not target outcome*

19 McKinley L, Kelton JM, Popovian R. Sowing confusion in the field: the interchangeable use of biosimilar terminology. Curr Med Res Opin 2019;35:619–21. 10.1080/03007995.2018.1560223 *not target outcome*

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21 Payne T. Biosimilar draft guidance issue by US FDA. Bioanalysis 2012;4:759–759. 10.4155/bio.12.67 *not target outcome*

22 Peterson J, Budlong H, Affeldt T, *et al.* Biosimilar products in the modern U.S. health care and regulatory landscape. JMCP 2017;23:1255–9. 10.18553/jmcp.2017.23.12.1255 *not target outcome*

23 Seungwon L. Ethical considerations on the biosimilar pathway. Published Online First: 2011.http://www.dbpia.co.kr/Journal/articleDetail?nodeId=NODE02256467 *not target publication status*

24 Singh SC, Bagnato KM. The economic implications of biosimilars. Am J Manag Care 2015;21:s331-340. *not target outcome*

25 Traynor K. Virginia passes nation's first biosimilar substitution law. Published Online First: 2013.https://academic.oup.com/ajhp/article-abstract/70/10/834/5112257. *not target publication status*

26 Vulto AG. [Biosimilar registered despite the Netherlands opposing vote: greater uncertainty about authorised drugs in the Netherlands]. Ned Tijdschr Geneeskd 2017;161:D1556–D1556. *not target outcome*

27 Webster PC. Canada's approach to biosimilars questioned. CMAJ: Canadian Medical Association Journal = Journal De L'association Medicale Canadienne 2015;187:1199–1199. 10.1503/cmaj.109-5169 *not target outcome*

28 Weise M. From bioequivalence to biosimilars: How much do regulators dare? Z Evid Fortbild Qual Gesundhwes 2019;140:58–62. 10.1016/j.zefq.2018.12.001 *not target outcome*

29 Wenzel RG. Current legal, regulatory, and scientific implications of biosimilars: Introduction. Am J Health Syst Pharm 2008;65:S1–S1. 10.2146/ajhp080209 *not target publication status*

30 Yale K, Awosika O, Rengifo-Pardo M, *et al.* Understanding state regulation of biosimilars and effect on prescribers. J Drugs Dermatol 2017;16:995–1000. *not target publication status*

31 Zeng D, Pan J, Hu K, *et al.* Improving the power to establish clinical similarity in a Phase 3 efficacy trial by incorporating prior evidence of analytical and pharmacokinetic similarity. J Biopharm Stat 2018;28:320–32. 10.1080/10543406.2017.1397012 *not target outcome, not target setting*

32 Zhai MZ, Sarpatwari A, Kesselheim AS. Why are biosimilars not living up to their promise in the US? AMA J Ethics 2019;21:E668-678. 10.1001/amajethics.2019.668 *not target outcome*

12.6 Characteristics of studies reporting on ELSO outcomes

Appendix table 7 Characteristics of studies reporting on ELSO outcomes

First author, year	CoI for at least one author	Industry funding	Study type	Countries	Domain focus
Dormuth *et al.*, 2020[111]	No	No info	Real-world experience/plans	Canada	Organisational
Dylst *et al.*, 2014[188]	No	No	Real-world experience/plans	Belgium	Organisational
Jensen *et al.*, 2019[191]	No info	No info	Real-world experience/plans	Denmark	Organisational
Mehr and Brook, 2017[247]	Yes	No	Real-world experience/plans	United States	Organisational
Moorkens *et al.*, 2019[112]	Yes	Yes	Real-world experience/plans	Sweden	Organisational
Moorkens *et al.*, 2019[113]	Yes	Yes	Real-world experience/plans	Sweden	Organisational
Rémuzat *et al.*, 2017[189]	Yes	Yes	Review	Europe	Organisational
Aerts *et al.*, 2014[248]	No	No info	Review	Europe	Legal/regulatory
Agence Nationale de Sécurité du Médicament et des Produits de Santé, 2016[249]	No	Not applicable	Q&A/explanation	France	Legal/regulatory
Agenzia Italiana del Farmaco, 2020[250]	Not applicable	Not applicable	Q&A/explanation	Italy	Legal/regulatory
Agenzia Italiana del Farmaco, 2018[251]	Not applicable	Not applicable	Guidance/position statement	Italy	Legal/regulatory
Al-Sabbagh *et al.*, 2016[252]	No info	Yes	Review	United States/Europe	Legal/regulatory
Bhatt, 2018[253]	No	Yes	Review	United States/Europe	Legal/regulatory
British Columbia Ministry of Health, 2020[254]	Not applicable	Not applicable	Q&A/explanation	Canada	Legal/regulatory
Bundesamt für Sicherheit im Gesundheitswesen, 2019[255]	Not applicable	Not applicable	Q&A/explanation	Austria	Legal/regulatory
Carver *et al.*, 2010[256]	Yes	No info	Review	United States	Legal/regulatory
Center for Drug Evaluation and Research, 2020[257]	Not applicable	Not applicable	Guidance/position statement	United States	Legal/regulatory
Center for Drug Evaluation and Research, 2019[206]	Not applicable	Not applicable	Guidance/position statement	United States	Legal/regulatory
Center for Drug Evaluation and Research, 2019[258]	Not applicable	Not applicable	Q&A/explanation	United States	Legal/regulatory
Center for Drug Evaluation and Research, 2017[259]	Not applicable	Not applicable	Q&A/explanation	United States	Legal/regulatory
Chance, 2018[260]	No	No	Review	United States	Legal/regulatory
Chapman *et al.*, 2016[261]	Yes	No info	Reflections	Multinational	Legal/regulatory

First author, year	CoI for at least one author	Industry funding	Study type	Countries	Domain focus
Chen *et al.*, 2018[262]	No	No	Review	United States	Legal/regulatory
Christl *et al.*, 2017[263]	Not applicable	No info	Review	United States	Legal/regulatory
College ter Beoordeling van Geneesmiddelen, 2015[264]	Not applicable	Not applicable	Q&A/explanation	Netherlands	Legal/regulatory
Daller, 2016[265]	No info	No info	Review	United States/Europe	Legal/regulatory
Dougherty *et al.*, 2018[266]	No	No info	Review	United States	Legal/regulatory
EMA, 2018[197]	Not applicable	Not applicable	Q&A/explanation	Europe	Legal/regulatory
EMA, 2014[115]	Not applicable	Not applicable	Guidance/position statement	Europe	Legal/regulatory
EMA, 2012[199]	Not applicable	Not applicable	Guidance/position statement	Europe	Legal/regulatory
EMA, 2007[267]	Not applicable	Not applicable	Guidance/position statement	Europe	Legal/regulatory
EMA, 2005[268]	Not applicable	Not applicable	Guidance/position statement	Europe	Legal/regulatory
Endrenyi *et al.*, 2019[204]	No info	No info	Review	United States	Legal/regulatory
Epstein, 2018[269]	Yes	Yes	Review	United States	Legal/regulatory
Falit *et al.*, 2015[270]	Yes	No info	Review	United States	Legal/regulatory
FDA, 2020[271]	Not applicable	Not applicable	Guidance/position statement	United States	Legal/regulatory
Feagan *et al.*, 2014[272]	Yes	No info	Review	Multinational	Legal/regulatory
Fimea, 2015[273]	Not applicable	Not applicable	Guidance/position statement	Finland	Legal/regulatory
Fimea, no date[274]	Not applicable	Not applicable	Guidance/position statement	Finland	Legal/regulatory
Gemeinsamer Bundesausschuss, 2020[275]	Not applicable	Not applicable	Guidance/position statement	Germany	Legal/regulatory
Gitter, 2011[276]	No info	No info	Review	United States	Legal/regulatory
Ha and Kornbluth, 2016[277]	Yes	No info	Review	United States	Legal/regulatory
Health Canada, 2016[278]	Not applicable	Not applicable	Guidance/position statement	Canada	Legal/regulatory
Heinemann *et al.*, 2015[279]	Yes	Yes	Review	Multinational	Legal/regulatory
Heled, 2019[280]	No	Not applicable	Reflections	United States	Legal/regulatory
Hung *et al.*, 2017[281]	Yes	No	Review	United States	Legal/regulatory
Juillard-Condat and Taboulet, 2018[282]	No info	No info	Review	France	Legal/regulatory
Kay, 2011[283]	No	No info	Review	United States	Legal/regulatory
Kirchhoff *et al.*, 2017[284]	Yes	Yes	Review	United States	Legal/regulatory

First author, year	CoI for at least one author	Industry funding	Study type	Countries	Domain focus
Lemery *et al.*, 2017[285]	No	No	Review	United States	Legal/regulatory
Li and Lobaina, 2017[286]	Yes	No info	Review	United States	Legal/regulatory
Lucio, 2018[287]	Yes	Yes	Review	United States	Legal/regulatory
Ministerio de Sanidad, Consumo y Bienestar Social, 2019[288]	Not applicable	Not applicable	Guidance/position statement	Spain	Legal/regulatory
NHS England, 2017[289]	Not applicable	Not applicable	Guidance/position statement	United Kingdom	Legal/regulatory
NHS England, no date[290]	Not applicable	Not applicable	Q&A/explanation	United Kingdom	Legal/regulatory
Nikolov and Shapiro, 2017[291]	No	No	Review	United States	Legal/regulatory
O'Callaghan *et al.*, 2019[203]	No	No info	Review	Multinational	Legal/regulatory
Olech *et al.*, 2016[292]	Yes	Yes	Review	Multinational	Legal/regulatory
Paradise, 2015[293]	No info	No info	Review	United States	Legal/regulatory
Paul-Ehrlich-Institut, 2019[294]	Not applicable	Not applicable	Guidance/position statement	Germany	Legal/regulatory
Rahalkar *et al.*, 2018[201]	No	No info	Review	Multinational	Legal/regulatory
Rathore and Bhargava, 2020[200]	No	No	Review	Multinational	Legal/regulatory
Rémuzat *et al.*, 2017[190]	Yes	Yes	Review	Europe	Legal/regulatory
Renwick *et al.*, 2016[295]	No	No info	Review	Multinational	Legal/regulatory
Scott *et al.*, 2015[296]	No info	No info	Review	Canada	Legal/regulatory
Sowinski-Raff, 2018[297]	No	No info	Review	United States	Legal/regulatory
Statens Legemiddelverk, 2017[219]	Not applicable	Not applicable	Guidance/position statement	Norway	Legal/regulatory
Stevenson, 2015[298]	Yes	Yes	Review	United States/Europe	Legal/regulatory
Swartenbroeckx *et al.*, 2014[299]	No info	No info	Review	Europe	Legal/regulatory
Swissmedic, 2020[172]	Not applicable	Not applicable	Guidance/position statement	Switzerland	Legal/regulatory
Swissmedic, 2020[300]	Not applicable	Not applicable	Guidance/position statement	Switzerland	Legal/regulatory
Swissmedic, 2020[193]	Not applicable	Not applicable	Guidance/position statement	Switzerland	Legal/regulatory
Swissmedic, 2020[176]	Not applicable	Not applicable	Guidance/position statement	Switzerland	Legal/regulatory
Therapeutic Goods Administration, 2018[301]	Not applicable	Not applicable	Guidance/position statement	Australia	Legal/regulatory
Tsiftsoglou *et al.*, 2013[302]	No	No info	Review	Multinational	Legal/regulatory
Tu *et al.*, 2019[303]	No	No	Reflections	Multinational	Legal/regulatory

First author, year	CoI for at least one author	Industry funding	Study type	Countries	Domain focus
Wang and Chow, 2012[304]	No info	No	Review	Multinational	Legal/regulatory
Webster and Woollett, 2017[305]	No	No	Reflections	Multinational	Legal/regulatory
World Health Organization, 2009[306]	Not applicable	Not applicable	Guidance/position statement	Multinational	Legal/regulatory
Wong *et al.*, 2017[307]	No	No	Review	United States	Legal/regulatory
Knoepffler, 2016[165]	No info	No info	Reflections	Multinational	Ethical
Murdoch and Caulfield, 2020[164]	No info	No info	Review	Canada	Ethical
Pipalava *et al.*, 2019[163]	No info	Yes	Review	United States/Europe	Ethical

Abbreviation: CoI, Conflict of Interest; ELSO, Ethical, Legal, Social, Organisational.

12.7 Regulatory/legal framework for biosimilars in different countries: additional countries

i. Australia

Key definitions: *Biosimilars* are defined as versions of an already registered biological medicine (the *reference product*).[301]

Approval process: The aim of the approval process is to establish the biosimilarity of the biosimilar relative to the reference product. The reference product must have been previously registered in Australia and must have been on the Australian market "for a substantial period"[301], which is determined individually for each case. When a reference product not licensed in Australia is used, it must have been approved by a regulatory agency with similar standards as the Australian body (the EMA and FDA are listed explicitly) and a bridging study must have demonstrated that the medication is indeed relevant for the Australian reference product.

Data requirements: Australian data requirements are explicitly based on European guidelines on quality, comparability, clinical and non-clinical data and product-specific guidelines.

Extrapolation: Extrapolation is regulated as by the EMA.[198]

Interchangeability and provisions for automatic substitution: Automatic substitution is permitted for "a-flagged" drugs. A-flagged drugs include biosimilars of TNF-alpha inhibitors.[308]

ii. Austria

Approval: Approval as part of the EMA's centralised procedure.

Interchangeability and provisions for automatic substitution: Automatic substitution is not permitted.

iii. Canada

Key definitions: *Biosimilars* are defined by Health Canada as a "biologic drug that obtains market authorization subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug"[278]. The *reference product* is defined as "a biologic drug authorized on the basis of a complete quality, non-clinical, and clinical data package, to which a biosimilar is compared to demonstrate similarity"[278].

Approval process: The approval process is designed to establish biosimilarity between the reference product and the biosimilar.[278] The assessment is based on the totality of structural, functional, non-clinical and clinical evidence.

The reference product must be approved in Canada. Non-Canadian drugs are eligible provided they have been demonstrated to be suitable for the submission.

Data requirements: Establishing the similarity in terms of quality attributes is the first step and involves the physicochemical and biological characterization as well as assessments of biological activity, immunochemical properties, purity, specifications and stability.[278] If similarity has been demonstrated for quality attributes, non-clinical *in vitro* (and possibly *in vivo*) studies are conducted. Specialized toxicological studies are not generally required. Clinical studies on PK and PD characteristics should be conducted, as should be efficacy trials. These studies should also assess safety and immunogenicity.

Extrapolation: Extrapolation to indications of the reference product is possible if scientifically justified.

Interchangeability and provisions for automatic substitution: Decisions on automatic substitution rests with provinces which are the public payers.[309] The province of British Columbia, for example, has switched all patients treated with certain biologics (including infliximab) for certain indications (including RA) to the respective biosimilar by November 2019 as part of its Biosimilars Initiative.[111] [254] By March 2020, all patients treated with the infliximab reference product for gastrointestinal indications were to be switched to an infliximab biosimilar. After the end of the transition phase, the province's drug benefit plan cut all funding to reference products and only covered biosimilars for infliximab (as well as etanercept and insulin glargine) for the included indications.

iv. France

Approval: Approval as part of the EMA's centralised procedure.

Interchangeability and provisions for automatic substitution: Automatic substitution is not generally permitted. There is a legal framework in place to allow automatic substitution for patients with specific conditions who initiate treatment if the treating physician does not explicitly forbid substitution.[185] [282] Drugs can substituted only within the same group. However, as of the time of writing, this framework is yet to be put into practice.

v. Germany

Approval: Approval as part of the EMA's centralised procedure.

Interchangeability and provisions for automatic substitution: Automatic substitution is currently not generally permitted. However, current law (§129 Paragraph 2 Sozialgesetzbuch V) specifies that, under certain conditions (e.g. drug prescribed only by substance name), pharmacies must choose among available drugs with the same substance, dosage, pack size, same or exchangeable galenic form, and same indications (under consideration of the Narcotics Law).[186] [310] The list of biologic drugs to which

these regulations apply have included the infliximab biosimilars Remsima® and Inflectra® since June 2015.[311]

The Federal Joint Committee has been tasked, in 2019, to develop guidance on automatic substitution by August 2022, in addition to developing guidance on physician-led substitution by August 2020.[186 275]

vi. Netherlands

Approval: Approval as part of the EMA's centralised procedure.

Interchangeability and provisions for automatic substitution: Automatic substitution is not permitted.

vii. Norway

Approval: Approval as part of the EMA's centralised procedure.

Interchangeability and provisions for automatic substitution: Automatic substitution is not permitted. A previous attempt by the Norwegian state to allow for automatic substitution of filgrastim was successfully challenged in court by the producer of the reference product.[217 219]

12.8 Overview of reviews of biosimilars

Appendix table 8 Non-systematic overview of biosimilar reviews

Review	Review aim	Systematic	Synthesis; endpoints	Drugs	Indications	Study designs	Author's conclusion
Bae and Lee, 2018[221]	Assess the relative efficacy and safety of infliximab biosimilar and infliximab reference product versus placebo (all with concomitant methotrexate) in individuals with active RA	No	NMA; ACR20 and serious adverse events (no time point specified)	Infliximab	RA	RCT	Biosimilar- [infliximab biosimilar] and originator-infliximab [infliximab reference product], in combination with MTX [methotrexate], represent effective interventions for active RA, with a low risk of SAEs [serious adverse events]. No significant difference between biosimilar- and originator-infliximab was found in terms of efficacy and safety. (p. 922)
Baji *et al.*, 2014[222]	Compare the efficacy and safety of infliximab biosimilar and other available biologicals for the treatment of RA	Yes	MTC; ACR20, ACR50 at week 24	Infliximab	RA	RCT	We found no significant difference between infliximab-biosimilar and other biological agents in terms of clinical efficacy and safety. (p. 53)
Bakalos and Zintzaras, 2019[235]	Collate information from switching studies regarding discontinuation rates of biosimilar mAbs and investigate the subjectivity of reasons for discontinuation to determine the impact of potential nocebo responses	Yes	Narrative: Biosimilar discontinuation rates and (subjective) reasons for discontinuation	Infliximab	IBD Rheumatic diseases Other autoimmune inflammatory diseases	RWE	Discontinuation rates of biosimilar mAbs may increase due to subjective effects after switching from an originator [reference product] mAb. These findings highlight the need for further patient education and well-designed, observational switching studies as well as the collection and analysis of identifiable pharmacovigilance and postmarketing data of biologics, including biosimilars. The collection of real-world results is particularly pertinent for mAbs other than CT-P13, for which there is currently a lack of observational switching data. (p. 155)
Barbier *et al.*, 2020[234]	Synthesize the available data on switching and assess if switching patients from a reference product to a biosimilar or vice versa affects efficacy, safety, or immunogenicity	Yes	Narrative; Efficacy, safety, and immunogenicity outcomes as well as author's conclusions/advice on switching (all in narrative form)	Adalimumab Epoetin Etanercept Filgrastim Follitropin Infliximab Insulin glargine Rituximab Somatropin Trastuzumab	Assisted fertility Cancer Chronic kidney disease and haemodialysis Diabetes Growth hormone deficiency IBD Rheumatic diseases	RCT RWE	No explicit authors' conclusion in abstract
Cohen *et al.*, 2018[233]	Evaluate the possibility that switching from a reference product to biosimilar could lead to altered clinical outcomes	Yes	Narrative; Efficacy, safety, immunogenicity outcomes (all in narrative form)	Adalimumab Epoetin Etanercept Filgrastim	Cancer Chronic kidney disease and end-stage renal disease Growth hormone deficiency	RCT RWE	While use of each biologic must be assessed individually, these results provide reassurance to healthcare professionals and the public that the risk of immunogenicity-related safety concerns

Review	Review aim	Systematic	Synthesis; endpoints	Drugs	Indications	Study designs	Author's conclusion
				Growth hormone Infliximab Rituximab	IBD Neutropenia Rheumatic diseases Other autoimmune inflammatory diseases		or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine. (p. 463)
Feagan *et al.*, 2019[131]	Investigate the evidence evaluating the safety and efficacy of switching between reference and biosimilar infliximab	Yes	Narrative; Efficacy, safety outcomes (all in narrative form)	Infliximab	Ankylosing spondylitis Morbus Crohn Plaque psoriasis Psoriatic arthritis RA Ulcerative colitis	RCT RWE	While available data have not identified significant risks associated with a single switch between reference and biosimilar infliximab, the studies available currently report on only single switches and were mostly observational studies lacking control arms. Additional data are needed to explore potential switching risks in various populations and scenarios. (p. 31)
Graudal *et al.*, 2019[225]	Compare effects of standard doses, high doses and low doses of TNF-alpha inhibitors on radiographic joint destruction in RA	Yes	NMA; Radiographically estimated joint destruction	Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	RA	RCT	No explicit authors' conclusion in abstract
Komaki *et al.*, 2017[223]	Evaluate efficacy and safety of biosimilars of TNF-alpha inhibitors relative to reference products in immune-mediated diseases	Yes	MA; ACR20, ACR50 at 12–16, 24—30, and 48–54 weeks, AEs	Adalimumab Etanercept Infliximab	Ankylosing spondylitis RA	RCT	In the present study, biosimilars of anti-TNF-alpha agents had an overall comparable efficacy and safety profile compared to their reference agents in RA and AS [ankylosing spondylitis] supporting their use for these conditions. (p. 4)
McKinnon *et al.*, 2018[100]	Conduct a systematic literature review of the outcomes of switching between biologics and their biosimilars and identify any evidence gaps	Yes	Narrative; Efficacy, safety, immunogenicity outcomes (all in narrative form)	Adalimumab Erythropoietin-simulating agents Etanercept Filgrastim Follicle-stimulating hormone Infliximab Insulin Rituximab	Diabetes Growth deficiencies IBD Renal anaemia Rheumatic diseases Other autoimmune inflammatory diseases Ovarian stimulation Undergoing chemotherapy	RCT RWE	There are important evidence gaps around the safety of switching between biologics and their biosimilars. Sufficiently powered and appropriately statistically analysed clinical trials and pharmacovigilance studies, with long-term follow-ups and multiple switches, are needed to support decision-making around biosimilar switching. (p. 27)
Numan and Faccin, 2018[130]	Assess the robustness and consistency of the current non-medical switching evidence, with a focus on TNF-alpha inhibitors	Yes	Narrative; Switching study design elements and discontinuation rates	Adalimumab Etanercept Infliximab	Ankylosing spondylitis Morbus Crohn IBD Psoriasis Psoriatic arthritis RA	RCT RWE	No explicit authors' conclusion in abstract

Review	Review aim	Systematic	Synthesis; endpoints	Drugs	Indications	Study designs	Author's conclusion
Odinet *et al.*, 2018[147]	Evaluate if patient and/or physician knowledge of a switch from a biologic reference product to a biosimilar is associated with an increase in adverse drug events likely to be susceptible to the nocebo effect	Yes	Narrative; Biosimilar discontinuation rates and reasons for discontinuation	Adalimumab Bevacizumab Etanercept Infliximab	IBD Rheumatic diseases Other autoimmune inflammatory diseases	RCT RWE	Current evidence is insufficient to confirm a biosimilar nocebo effect, although higher discontinuation rates in infliximab biosimilar open-label studies support this theory. Further studies are needed to evaluate the existence of a biosimilar nocebo effect. (p. 952)
Strand *et al.*, 2020[232]	Summarise immunogenicity data of biosimilars or biosimilar candidates for rheumatic diseases, plaque psoriasis, or IBD	Probably yes	Narrative; Anti-drug antibodies and neutralising antibodies in patients with anti-drug antibodies	Adalimumab Etanercept Infliximab Rituximab	IBD Plaque psoriasis Rheumatic diseases	RCT RWE	In conclusion, immunogenicity data of biosimilars or biosimilar candidates for TNF-alpha or CD20 inhibitors were collected in trials that varied in design and procedures for ADAb/nAb [anti-drug antibody/neutralising antibody] detection. In general, immunogenicity parameters of biosimilars are similar to those of their reference products. (p. 34)

Abbreviations: ACR, American College of Rheumatology; IBD, Inflammatory Bowel Diseases; MA, Meta-Analysis; mAb, Monoclonal Antibody; MTC, Mixed Treatment Comparison; NMA, Network Meta-Analysis; RA, Rheumatoid Arthritis; RCT, Randomized Controlled Trial; RWE, Real-World Evidence study; TNF, Tumour necrosis factor.
Note: Text in column "Review aim" is paraphrased. Synthesis methods as per authors' descriptions in the respective paper. In authors' conclusions, we spelled out explanations and added explanations of which term referred to the infliximab reference product and biosimilar, respectively, in square brackets (as the abbreviations used by study authors were often rather idiosyncratic).

12.9 RCT and RWE evidence base in scoping report and existing reviews

Appendix table 9 RCTs and RWE studies in scoping report and in existing reviews

Study in scoping review	Study design	Baji *et al.*, 2014[222]	Komaki *et al.*, 2017[223]	Bae and Lee, 2018[221]	Cohen *et al.*, 2018[233]	McKinnon *et al.*, 2018[100]	Numan and Faccin, 2018[130]	Odinet *et al.*, 2018[147]	Bakalos and Zintzaras, 2019[235]	Feagan *et al.*, 2019[131]	Graudal *et al.*, 2019[225]	Barbier *et al.*, 2020[234]	Strand *et al.*, 2020[232]
Yoo *et al.*, 2013[4]	RCT	x											x
Takeuchi *et al.*, 2015[126]	RCT		x	x									x
Yoo *et al.*, 2016[5]	RCT		x	x	x						x		
Choe *et al.*, 2017[121]	RCT		x		x								x
Jørgensen *et al.*, 2017[7]	RCT				x	x	x	x		x		x	x
Smolen *et al.*, 2017[125]	RCT			x									x
Tanaka *et al.*, 2017[129]	RCT				x	x	x	x		x		x	

Study in scoping review	Study design	Baji *et al.*, 2014[222]	Komaki *et al.*, 2017[223]	Bae and Lee, 2018[221]	Cohen *et al.*, 2018[233]	McKinnon *et al.*, 2018[100]	Numan and Faccin, 2018[130]	Odinet *et al.*, 2018[147]	Bakalos and Zintzaras, 2019[235]	Feagan *et al.*, 2019[131]	Graudal *et al.*, 2019[225]	Barbier *et al.*, 2020[234]	Strand *et al.*, 2020[232]
Yoo *et al.*, 2017[6]	RCT					x	x	x		x		x	x
Cohen *et al.*, 2018[122]	RCT												x
Smolen *et al.*, 2018[98]	RCT				x	x	x	x		x	x	x	x
Alten *et al.*, 2019[120]	RCT											x	
Goll *et al.*, 2019[128]	RCT						x			x			
Lila *et al.*, 2019[123]	RCT												
Matsuno *et al.*, 2019[124]	RCT												
Cohen *et al.*, 2020[127]	RCT												
Nikiphorou *et al.*, 2015[139]	RWE				x	x	x	x	x	x		x	
Glintborg *et al.*, 2017[135]	RWE				x	x	x	x	x	x			
Schmitz *et al.*, 2017[143]	RWE					x	x	x	x	x		x	
Vergara-Dangond *et al.*, 2017[144]	RWE				x		x	x		x		x	
Avouac *et al.*, 2018[133]	RWE						x	x	x	x		x	
Boone *et al.*, 2018[132]	RWE						x		x	x		x	
Glintborg *et al.*, 2018[134]	RWE									x		x	
Holroyd *et al.*, 2018[137]	RWE				x			x				x	
Scavone *et al.*, 2018[141]	RWE												
Scherlinger *et al.*, 2018[142]	RWE								x	x		x	
Tweehuysen *et al.*, 2018[117]	RWE				x	x	x		x	x		x	x
Grøn *et al.*, 2019[136]	RWE												
Layegh *et al.*, 2019[138]	RWE												
Nikiphorou *et al.*, 2019[140]	RWE												

Abbreviations: RCT, Randomized Controlled Trial; RWE, Real-World Evidence.
Note: Studies identified for the scoping review (rows) and existing reviews (columns) are ordered by year of publication, then alphabetically by surname of the first author. An “x” indicates that a study identified for the scoping review is included in the respective review. If an existing review had included an abstract or otherwise preliminary version of a by now full-text publication, we included the full-text publication for the respective review. Note that inclusion/exclusion criteria differed between existing reviews (see Appendix table 8), e.g. the studies by Baji *et al.*, Bae and Lee, and Komaki *et al.* did not include RWE studies.