Health Technology Assessment (HTA)

HTA Report

Title	**Infliximab reference product versus biosimilar for the treatment of rheumatoid arthritis**
Author/Affiliation	Mattli R.[1], Grobet C.[1], Sharakin M.[1], Pöhlmann J.[1], Vinci L.[1], Syleouni MA.[1], Carlander MJ.[1], Meier F.[1], Egli Ph.[2], Gerber-Grote A.[3], Wieser S.[1] [1]Winterthur Institute of Health Economics, Zurich University of Applied Sciences, Gertrudstrasse 15, 8401 Winterthur [2]Zentrum für Sozialrecht, Public Sector Zurich University of Applied Sciences, Gertrudstrasse 15, 8401 Winterthur [3]School of Health Professions, Zurich University of Applied Sciences, Katharina-Sulzer-Platz 9, 8400 Winterthur

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Executive Summary

Background: In Switzerland, relatively low biosimilar prescription rates have prompted the interest of the authorities. A health technology assessment (HTA) was requested to compare the available evidence of the infliximab reference product and its biosimilar for treating rheumatoid arthritis (RA).

Objective: This HTA examines the efficacy, effectiveness and safety of the infliximab biosimilar compared to its reference product in RA and presents the health economic impact of a potentially increased biosimilar utilization in Switzerland. Furthermore, ethical, legal, social and organisational aspects of treatment initiation with biosimilars or switching to biosimilars are analysed.

Research questions: Is it safe, efficacious and effective 1) to **initiate** treatment with infliximab biosimilar instead of the infliximab reference product, 2) to **switch** treatment from the infliximab reference product to infliximab biosimilar and 3) to **switch** treatment from infliximab biosimilar to the infliximab reference product in patients with RA?

Methods: A systematic literature search for evidence on efficacy, effectiveness, safety and health economic outcomes of the infliximab reference product compared to biosimilars in RA was conducted. Meta-analysis was performed for outcomes with sufficient available evidence. The certainty of evidence for relevant outcomes was assessed by applying the GRADE approach. A de novo health economic model was built to assess cost differences between a RA patient treated with infliximab reference product and a patient treated with its biosimilar using a lifetime time horizon. The potential budget impact for Switzerland was estimated over the next five years. The health economic analysis focused on drug costs. Additional physician time and lab tests that may be required related to the switch were also considered. Furthermore, a targeted search for evidence on biosimilar-related ethical, legal, social and organisational aspects was conducted and findings were summarized and discussed.

Results: We identified five randomized controlled trials (RCTs) which reported their results in nine publications, 17 real-world evidence (RWE) studies and 13 health economic studies. All included RCTs showed similar clinical efficacy and safety after treatment initiation with biosimilar compared to its reference product. The performed meta-analysis confirmed that there is no difference in efficacy and safety outcomes between treatment initiation with biosimilar and reference product. The certainty of evidence for the critical and important outcomes was judged as moderate to high. Two studies analysed switching from reference product to biosimilar compared to the continuation of reference product treatment. Both studies found comparable efficacy and safety outcomes (i.e. sim-

ilar number and severity of adverse events) between the analysed groups. Their certainty of evidence was judged as low to moderate. None of the identified studies reported on switching from biosimilar to the reference product.

A de novo cost-minimisation analysis showed that treatment initiation with infliximab reference product costs CHF 18'065 more per RA patient than treatment initiation with infliximab biosimilars over a lifetime time horizon. This cost difference is solely based on differences in drug costs. When considering uncertainty behind different model parameters, the difference in drug costs over a lifetime ranged between CHF 10'380 and CHF 23'342 per patient. The budget impact analysis assumed policy scenarios in which the price of the infliximab reference product would be decreased or the use of biosimilars promoted. Cost savings were estimated at CHF 1.58 million over 5 years for approximately 60 annual incident RA patients eligible for infliximab with a range between CHF 0.58 million and 4.78 million. Staying on the infliximab reference product costs CHF 17'812 more per patient than switching to the infliximab biosimilars over a lifetime time horizon (range: CHF 10'126 to CHF 23'088). This cost difference includes differences in drug costs as well as additional physician time and lab tests that may be required related to the switch. In the budget impact analysis savings related to switching to the biosimilar amounted to CHF 9.32 million over 5 years based on approximately 1'000 prevalent RA patients currently treated with the infliximab reference product. When considering uncertainty behind the eligible patient population and future treatment mix the budget impact ranged from CHF 2.20 million to CHF 17.30 million.

There were no severe nor highly controversial ethical issues identified based on the scientific evidence concerning treatment initiation with infliximab reference product vs. infliximab biosimilars or when switching from the reference product to biosimilars of infliximab in patients with RA. From a legal perspective, interchangeability of biologics is a key issue. Interchangeability of biologics in Switzerland is not explicitly regulated by neither the therapeutic products law nor the health insurance law. Currently, the decision about interchangeability in an individual case rests with treating physicians in compliance with their professional duties and due diligence. No evidence on social issues associated with the use of biosimilars were identified. Organisational issues may relate to policies to (not) promote and (not) implement biosimilars nationwide. Within this context, relevant are the profit margins that depend on the price of a product. As reference products have higher prices compared to biosimilars, there are financial incentives to use reference products instead of biosimilars.

Conclusion: Treatment initiation with infliximab biosimilar or switching to infliximab biosimilar showed comparable efficacy, effectiveness and safety compared to treatment initiation with the reference product or to continuation of reference product in patients with RA, respectively. The certainty of evidence for treatment initiation was judged moderate to high whereas for treatment switch it was low to moderate. Potential policy interventions reducing the price of the infliximab reference product or promoting the use of biosimilars could lead to cost savings of CHF 1.6 million for treatment initiation based on approximately 60 annual incident RA patients and CHF 9.3 million for treatment switch based on approximately 1'000 prevalent RA patients over five years.

Hintergrund: In der Schweiz kam das Interesse an einem Health Technology Assessment (HTA) des Infliximab-Referenzprodukts im Vergleich zu Biosimilars zur Behandlung der rheumatoiden Arthritis (RA) auf, da die Verschreibungsraten von Biosimilars relativ niedrig sind**.**

Ziel: Mit diesem HTA werden die Wirksamkeit, Effektivität und Sicherheit von Infliximab-Biosimilars im Vergleich zu ihrem Referenzprodukt bei RA beurteilt und die gesundheitsökonomischen Auswirkungen einer potenziell verstärkten Anwendung von Biosimilars in der Schweiz präsentiert. Zudem werden ethische, rechtliche, soziale und organisatorische Aspekte der Aufnahme der Behandlung mit Biosimilars oder des Switchings auf Biosimilars analysiert.

Forschungsfragen: Ist es sicher, wirksam und effektiv, 1) die Behandlung mit einem Infliximab-Biosimilar anstelle des Infliximab-Referenzprodukts **zu beginnen**, 2) die Behandlung mit dem Infliximab-Referenzprodukt auf ein Infliximab-Biosimilar **umzustellen** und 3) die Behandlung eines Infliximab-Biosimilars auf das Infliximab-Referenzprodukt bei Patienten mit RA **umzustellen**?

Methoden: Eine systematische Literaturrecherche nach Evidenz zu Wirksamkeit, Effektivität, Sicherheit sowie gesundheitsökonomischen Ergebnissen des Infliximab-Referenzprodukts im Vergleich zu Biosimilars bei RA wurde durchgeführt. Eine Metaanalyse der Ergebnisse erfolgte anhand der verfügbaren Evidenz. Die Sicherheit der Evidenz für relevante Ergebnisse wurde mittels des GRADE-Ansatzes beurteilt. Ein de-novo-gesundheitsökonomisches Modell wurde erstellt, um die Kostenunterschiede zwischen einem RA-Patienten, der mit dem Infliximab-Referenzprodukt behandelt wird, und einem Patienten, der mit dem Biosimilar behandelt wird, bei einem lebenslangen Zeithorizont zu beurteilen. Die potenziellen budgetären Auswirkungen für die Schweiz wurden für die nächsten fünf Jahre geschätzt. Der Fokus der gesundheitsökonomischen Analyse lag auf den Arzneimittelkosten. Die zusätzliche vom Arzt/von der Ärztin aufgewendete Zeit sowie Labortests, die im Zusammenhang mit dem Switching erforderlich werden können, wurden ebenfalls berücksichtigt. Ferner erfolgte eine gezielte Recherche nach Evidenz zu Biosimilar-bezogenen ethischen, rechtlichen, sozialen und organisatorischen Aspekten deren Ergebnisse zusammengefasst und diskutiert wurden.

Ergebnisse: Wir identifizierten fünf randomisierte kontrollierte Studien (RCTs), deren Ergebnisse in neun Publikationen publiziert wurden, 17 Real-World-Evidence-Studien (RWE) und 13 gesundheitsökonomische Studien. Alle eingeschlossenen RCTs zeigten ähnliche klinische Wirksamkeit und Sicherheit nach dem Beginn der Behandlung mit einem Biosimilar im Vergleich zu seinem Referenzprodukt. Die durchgeführte Metaanalyse bestätigte, dass sich die Wirksamkeits- und Sicherheitsergebnisse zwischen dem Beginn der Behandlung mit dem Biosimilar und dem Referenzprodukt nicht unterschieden. Die Sicherheit der Evidenz (certainty of evidence) für kritische und wichtige Ergebnisse wurde als mässig bis hoch eingestuft. Das Switching vom Referenzprodukt auf ein Biosimilar im Vergleich zur Fortsetzung der Behandlung mit dem Referenzprodukt wurde in zwei Studien analysiert. Beide Studien stellten in den untersuchten Gruppen vergleichbare Wirksamkeits- und Sicherheitsergebnisse (das heisst ähnliche Anzahl und Schwere der unerwünschten Ereignisse) fest. Ihre Sicherheit der Evidenz wurde als niedrig bis mässig eingestuft. Keine der identifizierten Studien befasste sich mit einem Switching vom Biosimilar zum Referenzprodukt.

Eine De-novo-Kostenminimierungsanalyse hat aufgezeigt, dass der Beginn der Behandlung mit dem Infliximab-Referenzprodukt bei einem lebenslangen Zeithorizont pro RA-Patient um 18'065 Franken höhere Kosten generiert als der Behandlungsbeginn mit Infliximab-Biosimilars. Dieser Kostenunterschied beruht ausschliesslich auf unterschiedlichen Arzneimittelkosten. Unter Berücksichtigung der Unsicherheit im Zusammenhang mit verschiedenen Modellparametern lag die Differenz der Arzneimittelkosten bei einem lebenslangen Zeithorizont zwischen 10'380 und 23'342 Franken pro Patienten. Die Budget-Impakt-Analyse ging von politischen Szenarien aus, bei denen der Preis des Infliximab-Referenzprodukts gesenkt oder der Einsatz von Biosimilars gefördert würde. Die Kosteneinsparungen wurden auf 1,58 Millionen Franken über 5 Jahre für etwa 60 jährlich hinzukommende RA-Patienten geschätzt, für die Infliximab eine Option darstellt, wobei die Spanne zwischen 0,58 Millionen Franken und 4,78 Millionen Franken lag. Die Fortführung der Behandlung mit dem Infliximab-Referenzprodukt führt bei einem lebenslangen Zeithorizont im Vergleich zum Switching auf Infliximab-Biosimilars zu Mehrkosten von 17'812 Franken pro Patienten (Spanne: 10'126 Franken bis 23'088 Franken). Diese Kostendifferenz umfasst Unterschiede bei den Arzneimittelkosten, die zusätzliche vom Arzt/von der Ärztin aufgewendete Zeit sowie Labortests, die im Zusammenhang mit dem Switching erforderlich werden können. In der Budget-Impakt-Analyse beliefen sich die Einsparungen durch das Switching auf das Biosimilar auf 9,32 Millionen Franken über 5 Jahre pro etwa 1'000 prävalenter RA-Patienten, die aktuell mit dem Infliximab-Referenzprodukt behandelt werden. Unter Berücksichtigung der Unsicherheit hinsichtlich der geeigneten Patientenpopulation und des zukünftigen Behandlungsmixes reichten die budgetären Auswirkungen von 2,2 Millionen Franken bis zu 17,3 Millionen Franken.

Auf der Grundlage der wissenschaftlichen Evidenz wurden keine schwerwiegenden oder hochgradig kontroversen ethischen Probleme bezüglich des Beginns der Behandlung mit dem Infliximab-Referenzprodukt im Vergleich zu Infliximab-Biosimilars oder des Switchings vom Referenzprodukt auf ein Infliximab-Biosimilar bei RA-Patienten festgestellt. Aus rechtlicher Perspektive ist die Austauschbarkeit von Biologika ein zentraler Aspekt. Die Austauschbarkeit von Biologika ist in der

Schweiz weder im Heilmittelgesetz noch im Krankenversicherungsgesetz explizit geregelt. Derzeit obliegt die Entscheidung hinsichtlich der Austauschbarkeit im Einzelfall den in Übereinstimmung mit ihren Berufs- und Sorgfaltspflichtenpflichten agierenden behandelnden Ärzten. Es wurde keine Evidenz zu sozialen Aspekten, die mit der Verwendung von Biosimilars zusammenhängen, identifiziert. Organisatorische Aspekte können mit Richtlinien im Zusammenhang stehen, die besagen, dass Biosimilars flächendeckend (nicht) zu fördern und (nicht) anzuwenden sind. In diesem Zusammenhang sind die vom Preis eines Produktes abhängenden Gewinnmargen relevant. Da die Preise für Referenzprodukte über denjenigen für Biosimilars liegen, gibt es finanzielle Anreize, Referenzprodukte anstelle von Biosimilars zu verwenden.

Fazit: Die Wirksamkeit, Effektivität und Sicherheit des Beginns der Behandlung mit dem Infliximab-Biosimilar oder des Switchings auf das Infliximab-Biosimilar waren im Vergleich zum Behandlungsbeginn mit dem Referenzprodukt bzw. zur Fortführung der Behandlung mit dem Referenzprodukt bei Patienten mit RA ähnlich. Die Sicherheit der Evidenz für den Beginn der Behandlung wurde als mässig bis hoch, für das Switching als gering bis mässig eingestuft. Potenzielle politische Interventionen, die den Preis des Infliximab-Referenzprodukts reduzieren oder die Verwendung von Biosimilars fördern, könnten über fünf Jahre zu Kosteneinsparungen in Höhe von 1,6 Millionen Franken für den Behandlungsbeginn auf der Basis von etwa 60 jährlich hinzukommende RA-Patienten und 9,3 Millionen Franken für das Switching der Behandlung auf der Basis von etwa 1'000 prävalenten RA-Patienten führen.

Résumé

Contexte : En Suisse, le nombre relativement faible de prescriptions de biosimilaires a suscité l'intérêt des autorités. Une évaluation des technologies de la santé (ETS) a été demandée pour comparer les preuves disponibles du produit de référence infliximab et de son biosimilaire pour le traitement de la polyarthrite rhumatoïde (PR).

Objectif : L'ETS examine l'efficacité (en conditions idéales et réelles) et la sécurité du biosimilaire de l'infliximab par rapport au produit de référence chez les patients atteints de PR. Elle décrit aussi l'impact qu'aurait, en Suisse, une augmentation du recours aux biosimilaires sur l'économie de la santé. Sont également analysés les aspects éthiques, légaux, sociaux et organisationnels liés au démarrage de traitements avec des biosimilaires ou au passage à ceux-ci en cours de traitement.

Questions de recherche : Chez les patients présentant une PR, est-il sûr et efficace 1) de **commencer** un traitement avec un biosimilaire de l'infliximab au lieu du produit de référence, 2) de **passer** du produit de référence à un biosimilaire de l'infliximab en cours de traitement et 3) de **passer** d'un biosimilaire de l'infliximab au produit de référence en cours de traitement ?

Méthodes : Une recherche bibliographique systématique a été menée pour identifier les preuves de l'efficacité, de la sécurité et de l'incidence, sur l'économie de la santé, de l'infliximab en compa-

raison avec des biosimilaires. Une méta-analyse a été effectuée concernant les aspects pour lesquels des données sont disponibles. Le degré de certitude a été évalué pour les aspects pertinents en appliquant l'approche GRADE. Un modèle économique *de novo* a été élaboré afin d'évaluer les différences de coût entre un patient PR traité avec le produit de référence et un patient traité avec un biosimilaire, à l'échelle de la vie du patient. L'impact budgétaire potentiel en Suisse a été estimé pour les cinq prochaines années. L'analyse économique s'est concentrée sur les coûts des médicaments. Les tests en laboratoire et le temps de travail supplémentaire des médecins, qui peuvent être nécessaires en cas de passage au biosimilaire, ont également été considérés. En outre, une recherche de preuves a été menée de manière ciblée concernant les aspects éthiques, légaux, sociaux et organisationnels liés au biosimilaire. Ses résultats sont synthétisés et font l'objet d'une discussion.

Résultats : Nous avons identifié cinq essais contrôlés randomisés (ECR), dont les résultats sont rapportés dans neuf publications au total, ainsi que 17 études fondées sur des preuves empiriques et 13 études portant sur les aspects économiques. Tous les ECR inclus relèvent une efficacité et une sécurité similaires lorsqu'un traitement est commencé avec un biosimilaire ou le produit de référence. La méta-analyse confirme l'absence de différence. Le degré de certitude concernant les aspects cruciaux est jugé modéré à élevé. Deux études comparent des patients qui passent au biosimilaire avec d'autres qui continuent leur traitement avec le produit de référence. Elles relèvent toutes deux une efficacité et une sécurité comparables (nombre et sévérité des événements indésirables) chez les deux groupes. Le niveau de certitude offert par ces études est jugé faible à modéré. Aucune des études identifiées n'inclut des cas de remplacement d'un biosimilaire par le produit de référence.

Une analyse de minimisation des coûts *de novo* montre que commencer le traitement avec le produit de référence plutôt qu'avec un biosimilaire coûte 18 065 francs de plus par patient PR, sur toute la vie de celui-ci. Ce chiffre se fonde uniquement sur les différences de coûts des médicaments. Si l'on prend en considération l'incertitude liée à divers paramètres du modèle, la différence en termes de coûts des médicaments est comprise entre 10 380 et 23 342 francs par patient, à l'échelle d'une vie. L'analyse d'impact budgétaire part de scénarios dans lesquels le prix du produit de référence serait abaissé ou l'utilisation de biosimilaires encouragée. Les économies sont estimées à 1,58 million de francs sur cinq ans pour environ 60 patients PR incidents éligibles à l'infliximab chaque année, la plage d'incertitude s'étendant de 0,58 million à 4,78 millions de francs. À l'échelle d'une vie, conserver le produit de référence coûte 17 812 francs de plus par patient que passer à des biosimilaires (plage : de 10 126 francs à 23 088 francs). Cette estimation inclut aussi bien les différences de coûts entre les produits que les tests en laboratoire et le temps de travail supplémentaire pour les médecins, qui peuvent être requis lors du changement. Selon l'analyse d'impact budgétaire, passer au biosimilaire permettrait une économie de 9,32 millions de francs sur cinq ans, pour environ 1000 patients PR prévalents actuellement traités avec le produit de référence. En tenant compte de l'incertitude concernant la population éligible et la part d'utilisation future des différents médicaments, l'impact budgétaire serait compris entre 2,20 et 17,30 millions de francs.

Les données scientifiques n'ont pas permis d'identifier de question éthique grave ou hautement controversée concernant la substitution du produit de référence par des biosimilaires de l'infliximab chez les patients PR, que ce soit en début ou en cours de traitement. Sur le plan juridique, l'interchangeabilité des biomédicaments est un point crucial. En Suisse, cette question n'est pas explicitement réglementée, ni dans la législation sur les produits thérapeutiques, ni dans celle sur l'assurance maladie. Actuellement, la décision est prise au cas par cas par le médecin chargé du traitement, qui est soumis à des devoirs professionnels et à une obligation de diligence. Aucun résultat de recherche n'a été recensé concernant les questions sociales liées à l'usage de biosimilaires. Sur le plan organisationnel, les problèmes pourraient être liés à des politiques visant à (ne pas) promouvoir et à (ne pas) mettre en place les biosimilaires au niveau national. Dans ce contexte, il faut considérer les marges bénéficiaires qui dépendent du prix d'un produit. Comme les produits de référence ont des prix plus élevés que les biosimilaires, il existe des incitations financières à les préférer à ces derniers.

Conclusion : Chez les patients PR, l'adoption d'un biosimilaire de l'infliximab en début ou en cours de traitement présente une efficacité et une sécurité comparable au démarrage d'un traitement avec le produit de référence ou au maintien de celui-ci pour les traitements entamés. Le degré de certitude des preuves est jugé modéré à élevé s'agissant de l'utilisation du biosimilaire dès le début du traitement. Il est faible à modéré pour ce qui est du changement de médicament en cours de traitement. Des politiques visant à réduire le prix du produit de référence ou à promouvoir l'utilisation de biosimilaires pourraient permettre d'économiser, sur cinq ans, 1,6 million de francs en ce qui concerne le choix du médicament en début de traitement, avec quelque 60 patients PR incidents par an, et 9,3 millions de francs s'agissant du changement de produit en cours de traitement, sachant qu'on dénombre environ 1000 patients PR prévalents.

Sintesi

Premessa: In Svizzera, il numero di prescrizioni di biosimilari relativamente basso hanno suscitato l'interesse delle autorità. È stato richiesto un health technology assessment (HTA) per confrontare le prove disponibili del prodotto di riferimento infliximab e del suo biosimilare per il trattamento dell'artrite reumatoide (RA).

Obiettivo: il presente HTA valuta l'efficacia, l'efficienza e la sicurezza del biosimilare di infliximab rispetto al prodotto di riferimento nel trattamento dell'AR e illustra l'impatto economico sul sistema sanitario del potenziale uso accresciuto del biosimilare in Svizzera. La valutazione comprende anche l'analisi degli aspetti etici, giuridici, sociali e organizzativi dell'avvio del trattamento con un biosimilare o del passaggio a un biosimilare durante il percorso terapeutico.

Quesiti della ricerca: è sicuro, efficace ed efficiente scegliere di 1) **iniziare** il trattamento con un biosimilare di infliximab anziché con un prodotto di riferimento infliximab? 2) **cambiare** il trattamento passando da un prodotto di riferimento infliximab a un biosimilare? 3) **cambiare** il trattamento passando da un biosimilare di infliximab al prodotto di riferimento infliximab per i pazienti AR?

Metodologia: è stata condotta una ricerca sistematica nella letteratura scientifica per cercare le prove di efficacia, efficienza e sicurezza e dell'impatto economico sul sistema sanitario del prodotto di riferimento infliximab rispetto ai biosimilari nel trattamento dell'AR. È stata effettuata una meta-analisi per valutare i risultati sulla base delle prove disponibili. La certezza dell'evidenza dei risultati rilevanti è stata esaminata con il metodo GRADE. È stato sviluppato un modello economico-sanitario *de novo* per valutare le differenze di costo sull'arco di una vita tra un paziente AR trattato con un prodotto di riferimento infliximab e uno trattato con un biosimilare. Il potenziale impatto economico per la Svizzera è stato stimato per il prossimo quinquennio. L'analisi economico-sanitaria era incentrata sui costi dei farmaci e prendeva in considerazione anche le ore di lavoro supplementare dei medici nonché le prove di laboratorio necessarie nell'eventualità di un cambio di trattamento. Inoltre, è stata condotta una ricerca mirata per identificare gli aspetti etici, giuridici, sociali e organizzativi connessi al ricorso a un biosimilare e i risultati sono stati sintetizzati e discussi.

Risultati: abbiamo individuato cinque studi controllati randomizzati (*randomized controlled trials*, RCT) che illustravano i loro risultati in nove pubblicazioni, 17 studi fondati su prove empiriche (*real-world evidence*, RWE) e 13 studi che hanno analizzato gli aspetti economico-sanitari. Tutti gli RCT inclusi evidenziavano un'efficacia e sicurezza clinica simile quando si inizia un trattamento con un biosimilare o con il prodotto di riferimento. La meta-analisi condotta ha confermato che non vi sono differenze in termini di efficacia e sicurezza. La certezza dell'evidenza relativa ai risultati critici e importanti è stata giudicata da moderata a elevata. Due studi hanno confrontato il passaggio dal prodotto di riferimento a un biosimilare rispetto al proseguimento del trattamento con il prodotto di riferimento. Entrambi gli studi hanno evidenziato un'efficacia e sicurezza comparabile (vale a dire un numero e una gravità simili di eventi avversi) nei gruppi analizzati. In questi termini, la certezza dell'evidenza è stata giudicata da bassa a moderata. Nessuno degli studi individuati trattava del passaggio da un biosimilare al prodotto di riferimento.

Una analisi *de novo* relativa alla minimizzazione dei costi ha evidenziato che, sull'arco di una vita, cominciare il trattamento con il prodotto di riferimento infliximab costa 18 065 franchi in più per paziente AR rispetto a cominciare il trattamento con un biosimilare. Questa differenza di costo si basa soltanto sulla differenza del costo dei farmaci. Se si considerano le incognite insite in diversi parametri di modello, sull'arco di una vita la differenza tra i costi dei farmaci si situa tra 10 380 e 23 342 franchi per paziente. L'analisi dell'impatto economico ipotizzava scenari in cui il prezzo del prodotto di riferimento infliximab calava o veniva promosso l'uso del biosimilare. I risparmi sono stati stimati a 1,58 milioni di franchi su cinque anni per circa 60 pazienti AR incidenti potenzialmente trattabili con infliximab, con una variazione compresa tra 0,58 e 4,78 milioni. Sull'arco di una vita, mantenere il trattamento con il prodotto di riferimento infliximab costa 17 812 franchi in più per paziente rispetto al passaggio a un biosimilare (variazione: da 10 126 a 23 088 franchi). Questa differenza di costo comprende sia le differenze nel costo dei farmaci sia le ore di lavoro supplementare dei medici nonché le prove di laboratorio necessarie nell'eventualità di un cambio di trattamento. Secondo l'analisi dell'impatto economico, passare al biosimilare permetterebbe di risparmiare

9,32 milioni di franchi su cinque anni basandosi su circa 1000 casi di pazienti AR prevalenti attualmente trattati con il prodotto di riferimento infliximab. Se si considera l'incertezza insita nella popolazione di pazienti potenziali e il futuro trattamento misto, l'impatto economico si attesta tra 2,20 milioni e 17,30 milioni di franchi.

Sulla base delle evidenze scientifiche riguardanti il confronto tra l'inizio del trattamento di pazienti AR con il prodotto di riferimento infliximab o con biosimilari, non sono state identificate questioni etiche gravi o molto controverse. Dal punto di vista giuridico, l'intercambiabilità dei biofarmaci è una questione chiave. In Svizzera, l'intercambiabilità di questi prodotti non è disciplinata espressamente né dalla legge sugli agenti terapeutici né dalla legge federale sull'assicurazione malattie. Attualmente, la decisione relativa all'intercambiabilità nei casi individuali spetta al medico curante nel rispetto dei propri obblighi professionali e della debita diligenza. Non sono state identificate evidenze di problemi sociali legati all'uso di biosimilari. Eventuali problemi organizzativi possono dipendere da politiche che prevedono di (non) promuovere e (non) utilizzare biosimilari a livello nazionale. In tale contesto, si rivelano importanti i margini di profitto subordinati al prezzo di un prodotto. Poiché i prodotti di riferimento hanno prezzi più elevati rispetto ai biosimilari, vi è uno stimolo finanziario nell'utilizzare i primi anziché i secondi.

Conclusione: iniziare il trattamento con biosimilari di infliximab o passare a biosimilari di infliximab comporta un'efficacia, un'efficienza e una sicurezza simili a quando si inizia o si prosegue il trattamento di pazienti AR con il prodotto di riferimento. La certezza dell'evidenza quando si inizia il trattamento con biosimilari è stata giudicata da moderata a elevata, mentre per il cambio di trattamento è stata giudicata da bassa a moderata. I potenziali interventi politici per ridurre il prezzo del prodotto di riferimento infliximab o per promuovere l'uso di biosimilari potrebbero permettere di risparmiare 1,6 milioni di franchi per l'inizio del trattamento su circa 60 pazienti AR incidenti all'anno e 9,3 milioni di franchi per il cambio di trattamento su circa 1000 pazienti AR prevalenti sull'arco di cinque anni.

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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
ARA	American Rheumatism Association
AS	Ankylosing Spondylitis
AxSpA	Axial Spondyloarthritis
b[o/s]DMARD	[Biological Originator/Biosimilar] Disease-Modifying Anti-Rheumatic Drug
CDAI	Clinical Disease Activity Index
CEA	Cost-Effectiveness Analysis
CMA	Cost Minimisation Analysis
COI	Conflict of Interest
COS	Core Outcome Set
CRP	C-Reactive Protein
csDMARD	Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug
CV	Coefficient of variation
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
Mio.	Million
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
SAE	Serious Adverse Event
SCQM	Swiss Clinical Quality Management Registry
SD	Standard Deviation
SDAI	Simplified Disease Activity Index
SL	Spezialitätenliste (list of drugs reimbursed by mandatory healthcare insurance in Switzerland)
SpA	Spondyloarthritis
SSC	Swiss Supreme Court
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event

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 report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in a HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact, legal, social, ethical and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

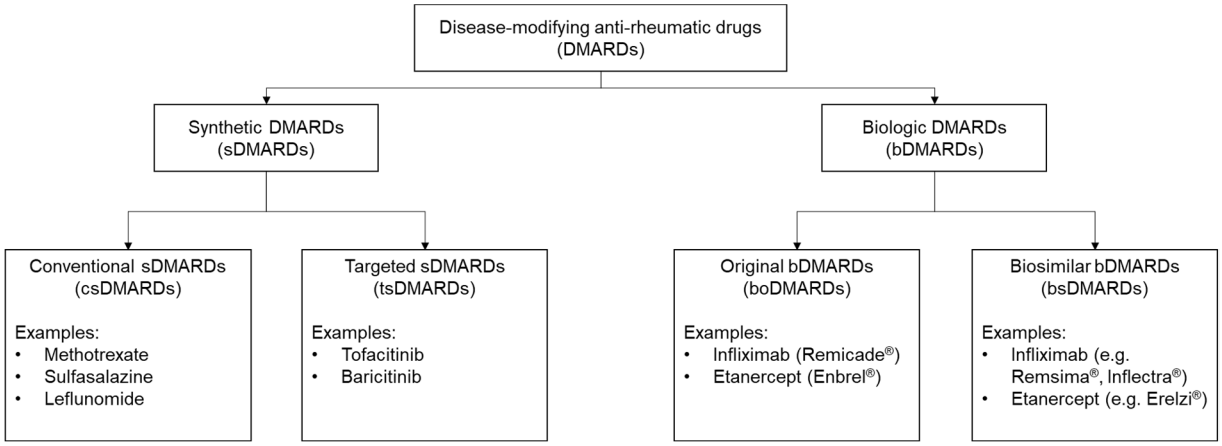
The biopharmaceutical infliximab is a monoclonal antibody (mAb) used to treat a number of inflammatory autoimmune diseases including rheumatoid arthritis (RA). In 2019, infliximab generated costs of around CHF 132 million, rendering it the second most cost-incurring drug reimbursed by the mandatory health 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. In Switzerland, the legal framework does not facilitate implementing similar policies. This HTA evaluates 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 question

This HTA report reviewed the evidence base on the safety, clinical efficacy and cost-effectiveness of the infliximab reference product compared 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.

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 compared 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 cause a loss of self-tolerance 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 C-reactive protein (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 Association (ARA), 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] With the current diagnostic criteria the indicated treatment at the appropriate timepoint can be determined. Early and evidence-based treatment of RA protects from joint damage and maintains mobility and quality of life.[20,21]

The typical patient initially presents a synovitis, i.e., one or more swollen, painful joints. A patient achieving a summary score of at least 6 according to the 2010 ACR/EULAR criteria (***Table 1***) and no other disease provides a plausible explanation, the patient 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
>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***).[22] A range of assessment instruments are available, including laboratory and imaging data and physician- or patient-reported outcome measures (PROMs) (***see Table 2***, which contains the most frequently used measures and those recommended by an ACR working group in their 2019 update).[22] For more information, also on feasibility of assessments, we refer the interested reader to the ACR working group review paper[22] and the ACR website on disease activity and functional status measurement, which provides forms and calculators for key disease activity measurements.[22,23]

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.[24,25]

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).[12,14,26] 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).[27] 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***)).[8,12,28]

Composite indices that assess disease activity based on PROMs also exist. Examples include the Patient Activity Scale, the Routine Assessment of Patient Index Data, and the Rheumatoid Arthritis Impact of Disease (RAID) score.[22,29–31] 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.[32] 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.[33]

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***).[34,35]

In addition to assessments of disease activity, radiologic damage should be examined.[14,36] Thereby, disease activity can be assessed and furthermore RA treatment efficacy can be documented by demonstrating maintained joint integrity. 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 disease activity assessment instruments

Assessment	Instrument/components	Cut-off points
RA COS assessments		
Acute phase reactant	C-reactive protein (CRP)[37]	—
Acute phase reactant	Erythrocyte sedimentation rate (ESR)[37]	—
Joint count	Tender joint count[38]	—
Joint count	Swollen joint count[38]	—
Patient global assessment	Usually measured with single question on VAS from 0–10 or 0–100[39]	—
Pain	Measured using VAS or numeric, multidimensional, verbal rating scales[40]	—
Physician global assessment	Usually measured on VAS from 0–10[41]	—
Functional status	Frequently measured using HAQ-DI (also known just as HAQ) or its derivatives, e.g. HAQ-II, MHAQ and MHDAQ[29,37,42]	—
Composite indices		
Disease activity	DAS28 (also DAS28-ESR)[43,44] • 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

Assessment	Instrument/components	Cut-off points
Disease activity	Simplified Disease Activity Index (SDAI)[27,43,45] • 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)[27,43] • 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
Disease activity	ACR/EULAR remission criteria[46] • SDAI • CDAI • Tender joint count (of 28) • Swollen joint count (of 28) • Patient global assessment (cm) • CRP (mg/dL)	Remission: • SDAI≤3.3 • CDAI≤2.8 • Tender joint count≤1 • Swollen joint count≤1 • Patient global assessment≤1 • CRP≤1
Disease activity, based on patient-reported outcomes	Patient Activity Scale-II (PAS-II)[22,29] • HAQ-II (0−10) • Pain (cm) • Patient global assessment (cm)	• 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
Disease activity, based on patient-reported outcomes	Routine Assessment of Patient Index Data 3 (RAPID3)[22,31] • MDHAQ (0−10) • Pain (cm) • Patient global assessment (cm)	• Remission: RAPID3≤3 • Low disease activity: 4≤RAPID3≤6 • Moderate disease activity: 7≤RAPID3≤12 • High disease activity: RAPID3≥13

<table>
<tr><th>Assessment</th><th>Instrument/components</th><th>Cut-off points</th></tr>
<tr><td>Change in status (primarily used in clinical trials; considered obsolete[9])</td><td>EULAR response criteria[34]
• 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[35,47,48]
• 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% compared 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[49]</td><td>—</td></tr>
<tr><td>Radiological damage</td><td>Various scoring methods to assess joint damage[36]</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.[25] 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.[8,12,28,46,50] Overall, treatment of RA should prevent and stop damage to joints and preserve function.[12,51,52]

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[50] (please note that, at the time of writing in January 2021, the 2020 ACR Guideline was in the process of being peer-reviewed and not yet publicly available[23]), and German guidelines for management of early RA[53] 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.[54]

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.[8,9,50,53]
- 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"[50] 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.[14,53,55] These drugs do not modify the disease.
- DMARD therapy should be started as soon as RA is diagnosed.[8,9,26,53] Early treatment initiation has been shown to be associated with improved long-term outcomes. DMARD initiation within 1 year, compared to 1 to 5 years, of symptom onset was associated with reduced long-term rates of radiographic progression.[56 9,53]
- Patients should be treated to the target of sustained disease remission, e.g. as defined by ACR/EULAR criteria (***Table 2***).[8,9,50,53] 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.[8,9,53]
- The first treatment strategy should include the csDMARD methotrexate.[8,9,50,53] 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.[8,9,53] 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.[8,14,50]
- 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.[50] 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.[8,9,50]
- 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.[8,26]

Legitimate scientific questions remain on the exact mechanism of action of all DMARD and their interaction in the recommended treatment regimens. Unquestionable, however, is the progress in efficacy of

pharmacotherapeutic treatment modalities and, therefore, the overall effectiveness in management of the disease RA over the last 20 years.

The introduction of biologicals, of which infliximab was the first one for RA, has dramatically changed the outcome of its treatment and considerably improved the treatment success.[57] However, open questions remain on how to increase the share of RA patients achieving a sustained remission, the optimal timing of escalation steps and how to de-escalate..[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.[14,53,58] 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.[59–63] 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.[61,64] The risk of developing RA is increased twofold in women (lifetime risk approximately 3.6%) compared to men (lifetime risk approximately 1.7%).[61,65] Similarly, the risk of developing RA increases with age, with mean disease onset between 55-65 years.[59,61]

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% compared to the general population, with higher risk in patients with persistently high disease activity.[66,67] This increased mortality has been attributed not only to RA activity but also to elevated risks of comorbidities among patients with RA.[61,67–69] In particular, the risk of cardiovascular diseases, diabetes, osteoporosis and infections is increased in patients with RA compared to the general population.[14,67,68,70] Treatment with TNF-alpha inhibitors such as infliximab is associated with reduced mortality compared to treatment with csDMARDs.[66] In

general, the introduction of biologics for the treatment of patients with RA has been associated with the potential to reduce disease burden for patients and society. Treatment itself may be associated with adverse events (AEs), such as infection in general, drug hypersensitivity reactions ranging from injection site reactions to severe infusion reactions or tuberculosis (with some TNF inhibitors).[14,71,72]

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.[73] 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.[73]

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.[74] 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. 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 in 2011.[75] 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).[76]

RA is also associated with considerable productivity losses, in particular due to disability-related productivity losses.[68,77] 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.[75] 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).[76]

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.[78] Biologic drugs are large, complex, heterogeneous molecules compared to chemically synthesized small-molecule drugs, which makes them difficult to manufacture.[78,79] Importantly, as biologics are produced by living organisms, they change from batch to batch.[78–81] 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”[82].

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.[79,83] Similar to their reference products, there may be batch-to-batch variation in biosimilar production.[80] Like generic drugs, biosimilars are usually priced lower than their respective reference products.[84]

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), spondyloarthritis

(SpA) 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.[78,85] 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.[85]

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.[57] 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.[57,86] 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.[86]

Infliximab is administered as an intravenous (IV) two-hour infusion.[87] 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.[10,87] 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.[10,88] Infliximab is given with concomitant methotrexate. Infliximab is contraindicated in patients with:[10,87]

- 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 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.[54,87,89,90]

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[91], have been included in the SL since October 2016.[92] In RA, use of infliximab is limited (*limitatio*) to patients with active RA after failure of prior standard therapy with DMARDs.[92]

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.[54] 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.[92]

Currently (January 2021), public list prices for 100 mg of infliximab are CHF 830.90 for the reference product and CHF 627.25 for the biosimilars.[92] In 2019, estimated total costs for infliximab were CHF 132 million, equivalent to 1.7% of estimated total drug costs in Switzerland, with an estimated 6,879 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).[1] The reference product accounted for an estimated 77.9% of all infliximab purchases.

4.2 Alternative technologies to infliximab

This HTA report is about comparing the infliximab reference product and the infliximab biosimilar. However, there are alternatives to infliximab for the treatment of RA, which we present here for the sake of completeness. Recently, many new bsDMARDs and tsDMARDs have become available for RA patients, which are equivalent in the treatment recommendations of the EULAR.[93] According to Swiss health insurance claims data, use of infliximab has decreased in recent years.[1,94,95]

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"[57] the treatment of RA in the past decades (***see Section 3.2***).[14] The five TNF-alpha inhibitors are generally clinically efficacious and show slow radiographic progression, with relatively little difference in efficacy between agents although head-to-head comparisons are sparse.[12,57]

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.[55] 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.[96,97]
- Abatacept, a fusion protein inhibiting T lymphocytes.[98]
- B-cell inhibitors, including rituximab.
- Janus kinase inhibitors, including tofacitinib, baricitinib and upadacitinib.[99] These are not biologics but small molecules.

4.3 Regulatory status / provider

Remicade® (infliximab reference product) received regulatory approval in Switzerland in 1999.[100] The two infliximab biosimilars approved in Switzerland (Inflectra® and Remsima®) received regulatory approval in 2015.[100] In RA, use of infliximab is limited (*limitatio*) to patients with active RA after failure of prior standard therapy with DMARDs.[92] 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.[92]

Other infliximab biosimilars not approved by Swissmedic include:

- PF-06438179/GP1111 (Zessly®; Ixifi®) approved in EU and USA
- SB2 (Flixabi®) approved in EU, USA and (Renflexis®) in South Korea
- ABP 710 approved in USA
- NI-071 approved in Japan
- BCD 0555 (Biocad Russian) approved in India and Russia

This HTA focuses on biosimilars approved in either Switzerland, EU or USA. Results from studies investigating biosimilars only approved in Japan (NI-071) and Russia/India (BCD 0555) will only be presented in the appendix.

5 PICO

The scoping report and the research questions 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 scoping report.

The scoping report showed the absence of evidence on PICO 3. Therefore, PICO 3 will not be further addressed in this HTA.

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 ($C_{min/trough}$, C_{max}) and pharmacodynamic outcomes, including acute phase reactants *Patient-reported outcome measures*: Functional status (HAQ-DI); patient global assessment; physician global assessment (grouped here for consistency though not technically a patient-reported outcome); pain *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; 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

Please 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 the reference product was treated as the intervention.

6.1 Specific questions based on central research questions

The central research questions focus on (clinical) efficacy, effectiveness, safety and cost-effectiveness. The main aim of the HTA is therefore to answer, for patients initiating infliximab biosimilars or switching from the reference product to infliximab biosimilar, the following questions:

- What is the clinical *efficacy* of the infliximab reference product compared 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"[101]. 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 compared to the reference product but to demonstrate equivalence.[102–104] Equivalence means that differences between treatments are clinically irrelevant.
- What is the *effectiveness* of the infliximab reference product compared 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).
- What is the *safety* of the infliximab reference product compared 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).[105] 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 compared to infliximab biosimilar in Switzerland and of the switch from one to the other? Health economic con-

siderations include cost-effectiveness analysis (CEA), i.e. the assessment of at least two treatments with regard to their effectiveness in relation to their cost.[106] 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:[107–110]

- 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.[111,112]
- 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.[110,113]
- 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.[107]
- 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.[114–116]

6.2 Additional questions

In agreement with the FOPH, we included additional outcomes that were considered relevant for (infliximab) biosimilars:

- What is the *pharmacokinetic* (PK), *pharmacodynamic* (PD) and *immunogenicity* profile of the infliximab reference product compared 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 also considered PK, PD and immunogenicity results.[82,117,118]

- 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). 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***).[39,41] 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).[119,120]
- 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.[119,120] We therefore considered treatment discontinuation (or retention) rates in RWE studies to be a relevant outcome, not least with regard to potential health economic modelling of infliximab biosimilars.

7 Effectiveness, efficacy and safety

7.1 Methodology effectiveness, efficacy and safety

7.1.1 Databases and search strategy

7.1.1.1 Search strategies and data sources

We developed search strategies based on the PICO criteria in collaboration with a medical librarian (***see Appendix 13.1***). Our focus was on the PIC components, and we did not specify outcomes to avoid undue narrowing of search results. This was also the reason why we combined the search for evidence on efficacy, safety and effectiveness with the one for health economic outcomes.

The search strategies were implemented by the medical librarian in Cochrane Library, Medline (via EBSCOhost), Embase, EconLit (via EBSCOhost) and PsycInfo (via EBSCOhost). The final search was conducted on 22 October 2020.

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 13.2***). 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 7.1.1.3***) were searched for additional relevant studies that had not previously been included.

In addition, we searched for ongoing RCTs on clinicaltrials.gov.

7.1.1.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria were defined according to PICO 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. We did not specify concrete outcomes as inclusion or exclusion criteria as long as outcomes were within the domains outlined in the PICO.

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.

Target countries included:

- Switzerland as the primary country of interest for the 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 and health economic analyses

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 and full health economic evaluations, including cost-minimisation analyses	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	Any other intervention
Study comparator	• Initiate treatment with biosimilar + methotrexate • Switch to infliximab biosimilar + methotrexate • Biosimilar approved in either Switzerland, EU or USA	Any other comparator Biosimilars only approved in Japan (NI-071) and Russia/India (BCD 0555) were not further considered in the full HTA
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.

7.1.1.3 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 HTA 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.[121]

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.

7.1.2 Assessment of quality of evidence

7.1.2.1 Risk of bias

We assessed the risk of bias according to the Cochrane handbook.[122] If a study described an adequate method in a specific risk of bias domain (e.g. adequate generation of random sequence for randomisation), it was judged as “low risk of bias” in this domain. Description of an in-adequate method was judged as “high risk of bias” and, if incomplete information was given, as “unclear risk of bias”. Two reviewers separately performed the assessment and inconsistencies were solved by consensus. Where consensus could not be found, a third reviewer was consulted.

7.1.2.2 GRADE assessment

To obtain an overall rating of confidence in estimates of effects, two reviewers applied the GRADE approach and rated the certainty of evidence of effect for relevant outcomes separately.[123] For the specific question under study, we specified the decision rule for judging the GRADE item "inconsistency" as serious, if heterogeneity in statistical meta-analysis was at least substantial (i.e. I^2 at least 50 to 90%). The GRADE evidence table was derived using the online tool (https://gdt.gradepro.org).

7.1.3 Methodology data analyses efficacy, effectiveness and safety

At the request of the FOPH, we focussed our systematic literature search on primary studies.

We conducted a *de novo* synthesis of RCTs. This allowed us to obtain a synthesis using inclusion/exclusion criteria approved by the FOPH and include the most recent evidence, e.g. recent studies that were not available to existing systematic reviews.[124–126]

We performed a quantitative synthesis, i.e. a meta-analysis, for PICO 1 separately for those outcomes with highest relevance for the patients and which were most frequently reported by RCTs and were judged as critical outcomes. Endpoints included ACR criteria for efficacy, AE rates for safety, and patient reported functional status (***Table 7***). The meta-analysis was conducted using the random effects model [127] and implemented by the metan-command of Stata.[128,129] Study heterogeneity were characterized using I^2 and standard assessments for publication bias and effects of small studies were performed.[130–132] Binary data were pooled using risk ratios (RR) and odds ratio (OR). Continuous data were pooled using weighted mean differences. Uncertainty was expressed using 95% confidence intervals. For statistical hypothesis testing, a significance level of 0.05 was used.

Outcome parameters for immunogenicity, PK/PD outcomes, and for those efficacy, safety and PROM outcomes that were not included in the meta-analysis (***Table 7***) and were reported in at least two RCTs as well as the outcomes for PICO 2 were summarized in a descriptive manner. Data on HRQoL for example were not presented, because only one RCT reported on this outcome measure.

The outcomes of each study were exported into MS Excel by one researcher and verified by a second researcher. Inconsistencies were solved by consensus. Where authors presented results for both, the intention-to-treat population as well as the per-protocol population, we included the intention-to-treat results in our analyses.

Therapy discontinuation and nocebo effects based on RWE studies were tabularized.

Table 7 Outcome analyses

Analyses	Outcome	Outcome category
Meta-analysis	Clinical efficacy: • ACR20 / ACR50 / ACR70 • HAQ-DI (PROM)	Critical
	Safety: treatment-emergent adverse events	Critical
	Clinical efficacy: • SDAI • CDAI • EULAR response • DAS28-CRP and -ESR	Important
	Safety: treatment-emergent serious adverse events	Important
Narrative synthesis	Immunogenicity • ADAb • NAb	Outcome
	PK/PD: • C min/trough • acute phase reactant • C max • T max • PTF • C avg	Outcome
	PROM • patient global assessment • physician global assessment • pain	Outcome
	Safety: • adverse events • serious adverse events	Outcome

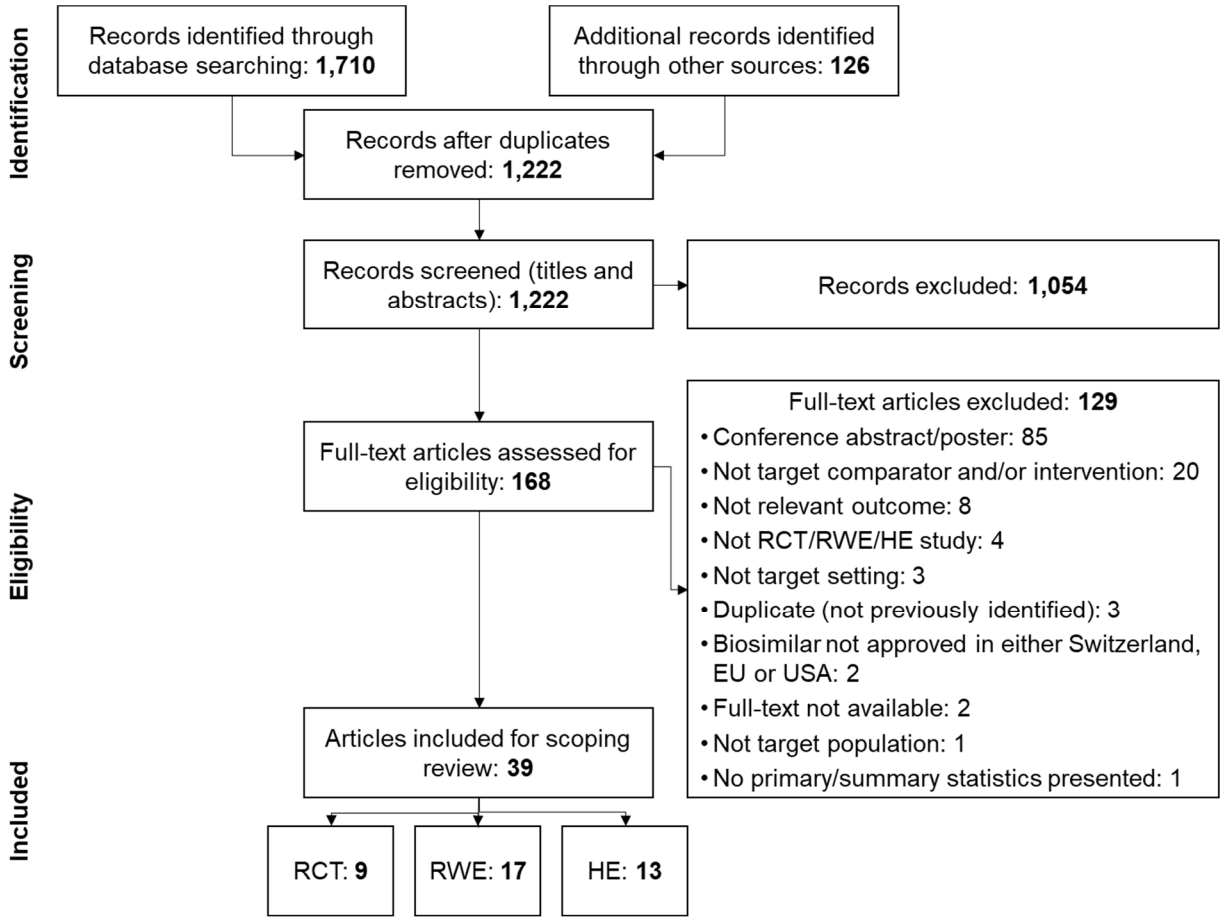
Abbreviations: ACR, American College of Rheumatology; ADAb Anti-Drug Antibody; AE, Adverse Event; CDAI, Clinical Disease Activity Index; CRP, C-Reactive Protein; DAS, Disease Activity Index; ESR, Erythrocyte Sedimentation Rate; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire Disability Index; NAb, Neutralizing Antibodies; PD, Pharmacodynamic; PG, Parallel-Group; PK, Pharmacokinetic; PROM, Patient-Reported Outcome Measure; SDAI, Simplified Disease Activity Index

7.2 Results effectiveness, efficacy and safety

7.2.1 PRISMA flow diagram

Of the 1,222 unique hits, 1,054 were excluded during title-abstract screening (***Figure 2***). Of the remaining 168 articles whose full texts were screened, 129 were excluded, most frequently because they were conference abstracts/posters or because they did not include information on infliximab biosimilars (***see Section 13.4.1***). Two studies were excluded, because the biosimilar under investigation is not approved in either Switzerland, EU or USA. Nevertheless, in ***Appendix 13.6.4*** (***Figure A 12 -Figure A 21***) the results of the extended meta-analysis including these two studies are shown. . Finally, 39 articles were retained for the HTA report, including 9 publications reporting on RCTs, 17 RWE studies and 13 health economic analyses. The health economic analyses will be further addressed in chapter 8.

Figure 2 Prisma flow diagram



Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[133]

7.2.2 Evidence table

7.2.2.1 Evidence table for RCTs

Nine publications reporting on five RCTs, including their extensions, were identified (***Table 8***).[4,5,102,134–139] Overall n=2499 rheumatoid arthritis patients were included. Seven publications reported results for PICO 1 and two for PICO 2. By publication date, the first was from 2013[4] and the most recent from 2020[139].

Countries, settings: Most RCTs were multinational, with the exception of one RCT from Japan.[138] All studies had a parallel-group design.

Indications: As per our inclusion criteria, all RCTs included (only) patients with RA.

Switch: Two RCTs investigated a switch to infliximab biosimilar compared to maintenance on the reference product.[102,134]

CoI (Conflict of Interest) and funding: All studies included had at least one author with a CoI. All studies were funded by the pharmaceutical industry.

Follow-up, sample size, age and sex: Follow-up periods were 22, 30 or 54 weeks for PICO 1 and 54 or 78 weeks (both with a duration of 24 weeks after the switch) for PICO 2. Sample sizes ranged from 101 participants[138] to 650 participants[135]. All RCTs recruited both women and men, with 80.4% (2009 of 2499) female participants. Participants' minimum age was between 18 and 20 years in all trials. All trials that specified a maximum age for inclusion used 75 or 80 years. The mean age of patients varied from 50 to 54.9 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. For all trials, only participants with at least 12 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, as their primary endpoints. Exceptions was the Japanese trial by Takeuchi *et al.*[138], which specified a PK endpoint (C_{max}) as its primary endpoint.

Table 8 Characteristics of included RCTs

First author, year	Trial name	Publication source	Countries	RCT design	Switch assessed	Follow-up (weeks)	Total sample size	Indications	Age (years) eligible	Intervention	Comparator	Primary endpoint
Yoo *et al.*, 2013[4]	PLANETRA	Annals of the Rheumatic Diseases	Multinational	PG	No	30	606	RA	18 to 75	Biosimilar	Reference product	Clinical efficacy (ACR20)
Yoo *et al.*, 2016[5]	PLANETRA	Arthritis Research & Therapy	Multinational	PG	No	54	455	RA	18 to 75	Biosimilar	Reference product	Clinical efficacy (ACR20)
Takeuchi *et al.*, 2015[138]	JapicCTI-111620	Modern Rheumatology	Japan	PG	No	54	101	RA	20 to 75	Biosimilar	Reference product	PK/PD (C max)
Choe *et al.*, 2017[136]	EudraCT	Annals of the Rheumatic Diseases	Multinational	PG	No	30	584	RA	18 to 75	Biosimilar	Reference product	Clinical efficacy (ACR20)
Smolen *et al.*, 2017[137]	EudraCT	Rheumatology	Multinational	PG	No	54	505	RA	18 to 75	Biosimilar	Reference product	Clinical efficacy (ACR20)
Smolen *et al.*, 2018[102]	EudraCT	Annals of the Rheumatic Diseases	Multinational	PG	Yes	78	396	RA	18 to 75	Switch to biosimilar and continued biosimilar	Continued reference product	Clinical efficacy (ACR20)
Cohen *et al.*, 2018[135]	REFLECTIONS	Arthritis Research & Therapy	Multinational	PG	No	30	650	RA	>=18	Biosimilar	Reference product	Clinical efficacy (ACR20)
Alten *et al.*, 2019[134]	REFLECTIONS	RMD Open	Multinational	PG	Yes	54	566	RA	>=18	Switch to biosimilar and continued biosimilar	Continued reference product	Clinical efficacy (ACR20)
Genovese et al., 2020[139]	Genovese	Arthritis Research & Therapy	Multinational	PG	No	22	558	RA	18 to 80	Biosimilar	Reference product	Clinical efficacy (ACR20)

Abbreviations: ACR, American College of Rheumatology; AE, Adverse Event; ESR, Erythrocyte Sedimentation Rate; PD, Pharmacodynamic; PG, Parallel-Group; PK, Pharmacokinetic; RA, Rheumatoid Arthritis; RCT, Randomized Controlled Trial

7.2.2.2 Not yet published and ongoing clinical trials

We identified in clinicaltrials.gov some completed but not yet published and ongoing RCTs related to the topic of this HTA (***Table 9***).

Table 9 Not yet published and ongoing RCTs identified in clinicaltrials.gov

NCT Number	Title	Status
NCT02990806	A Phase 3 Study of NI-071 in Patients With Rheumatoid Arthritis (RADIANCE)	Completed in 2019 with 683 participants; results not yet published
NCT01567358	Study of NI-071 in Comparison With Remicade in Patients With Rheumatoid Arthritis	Completed in 2013 with 14 participants; results not published
NCT03478111	CMAB008 With MTX Therapy in Adult Patients With Moderately to Severely Active Rheumatoid Arthritis	Completed in 2019 with 390 participants; results not yet published
NCT03707535	To Compare the Efficacy, Pharmacokinetics and Safety Between CT-P13 and China Approved Remicade When Co-administered With Methotrexate in Patients With Active Rheumatoid Arthritis	Active, not recruiting
NCT04178850	Clinical Comparative Study to Evaluate the Efficacy and Safety of Recombinant Anti-TNF-alpha Antibodies for Injection	Recruiting

7.2.2.3 Evidence table for RWE studies

Seventeen RWE studies were identified as relevant (***Table 10***).[120,140–155]

CoI and funding: Not all studies reported on CoI and study funding. Where such information was available, several 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 7.1.1.2***). Of the included studies, four were performed in the Netherlands and three in Denmark, with the remainder from Canada, Finland, France, Italy, Spain, UK and the US. No study was identified for Switzerland. Most studies were set in hospitals and other medical facilities while three studies used register data and two studies analysed state- or nationwide data. Studies were split evenly between prospective and retrospective studies.

Indications: One study was conducted in an RA-only population.[144] 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. Nine 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.[144] 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 product.[142,150] One study compared a policy cohort with three historical cohorts to evaluate changes in health care services utilization after the policy (i.e. switch from reference product to biosimilar) was introduced.[154] 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; eight studies included less than 50 individuals with RA. However, there were also five studies with 200 individuals with RA or more.[142–144,153,154] With regard to age- and sex-related patient eligibility criteria, 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)[141,146,148,150], effectiveness (in particular DAS-28)[120,152], safety (adverse drug reactions)[149], immunogenicity (ADAbs)[142], and nocebo effect (measured as unexplained unfavourable outcomes)[140] outcomes as their primary outcomes. Two studies analysed the change in proportion of patients treated with the biosimilar versus the reference product after the introduction of a new policy.[154,155] In one study, the new biosimilar policy was implemented in one hospital[155], and in the other study, it was implemented in an entire state.[154] Another study described the utilization of the infliximab reference product and its biosimilar during the last 3.5 years in the United States.[153] 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 (RA)* sample size	Age (years) eligible	Primary endpoint	Subgroups
Avouac *et al.*, 2018[141]	No info	No info	France	Hospital	Prospective	AxSpA, Crohn, RA, UC, Uveitis, Other	Yes	Switched to biosimilar	34	260 (31)	Adult	Drug retention	No info
Boone *et al.*, 2018[140]	Yes	No info	Netherlands	Hospital	Prospective (some data retrieved retrospectively)	AS, Crohn, PsA, RA, UC	Yes	Switched to biosimilar	52	125 (9)	No info	Unexplained unfavourable effect	No info
Dutcher *et al.*, 2020[153]	No info	No	United States	Sentinel Distributed Database (Nationwide database)	Retrospective	Crohn, UC, AS, PsA, Pso, RA	No	Reference product vs. biosimilar	No follow-up. Longitudinal study over 3.5 years	72,908	Every age	Utilization of infliximab from January 2015 to August 2018 in the United States	No info
Fisher *et al.*, 2020[154]	No	No	Canada	Rapid monitoring analysis associated after policy introduction in British Columbia	Retrospective	Any rheumatologic diagnosis, RA, AS, PsA, Pso	No	Historical cohorts 2016, 2017, 2018 vs. Policy cohort	3 months after vs. 3 years before policy's introduction	1,744 (915)	Every age	Changes in health services utilization associated with the Biosimilars Initiative	No info
Glintborg *et al.*, 2018[142]	No info	Yes	Denmark	Hospital	Prospective	AxSpA, PsA, RA	Yes	Switched to biosimilar versus biosimilar in INX-naive	52	546 (282)	Adult	ADAb	Switchers; naive

First author, year	CoI for at least one author	Industry funding	Countries	Setting	Perspective	Indications	Switch assessed	Arms	Follow-up (weeks)	Total (RA)* sample size	Age (years) eligible	Primary endpoint	Subgroups
Glintborg *et al.*, 2017[143]	Yes	Yes	Denmark	Register	Retrospective	AxSpA, PsA, RA	Yes	Switched to biosimilar	52	802 (403)	Adult	No primary endpoint specified	Previous infliximab treatment; baseline remission status; withdrawn patients
Grøn *et al.*, 2019[144]	Yes	No info	Denmark	Register	Retrospective	RA	No	Biosimilar (certolizumab pegol and abatacept arms ignored)	52	225 (225)	Adult	Not applicable	Comorbidity; seropositive status; DAS28
Holroyd *et al.*, 2018[145]	Yes	No info	United Kingdom	Hospital	Retrospective	AS, PsA, Ra, Other	Yes	Switched to biosimilar	53	59 (29)	No info	No primary endpoint specified	No info
Layegh *et al.*, 2019[146]	No info	No info	Netherlands	Hospital/outpatient	Retrospective	PsA, RA	Yes	Switched to biosimilar	104	45 (41)	Adult	Drug retention	No info
Nikiphorou *et al.*, 2019[148]	Yes	Yes	Finland	Hospital	Retrospective	AS, IBD, JIA, PsA, RA, REA, SpA, Other	Yes	Reference product versus biosimilar (switch and naive)	104	395 (123)	No info	Drug retention	Timing of biosimilar initiation
Nikiphorou *et al.*, 2015[147]	No	Yes	Finland	Hospital	Prospective	AS, JIA, PsA, RA, REA	Yes	Switched to biosimilar	48	39 (15)	Adult	No primary endpoint specified	No info
Saxby *et al.*, 2020[155]	No	No	United Kingdom	Tertiary hospital	Prospective	Patients treated with infliximab reference product	Yes	Switched to biosimilar	54	260	No info	Number of patients who transferred from originator infliximab to its biosimilar	No info

First author, year	CoI for at least one author	Industry funding	Countries	Setting	Perspective	Indications	Switch assessed	Arms	Follow-up (weeks)	Total (RA)* sample size	Age (years) eligible	Primary endpoint	Subgroups
Scavone *et al.*, 2018[149]	No	No	Italy	Register	Retrospective	Crohn, Pso, RA, SpA, UC	No	Reference product versus biosimilar	104	459 (156)	No info	ADR	No info
Scherlinger *et al.*, 2018[150]	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 (37)	No info	Drug retention	No info
Schmitz *et al.*, 2017[151]	No	No	Netherlands	Hospital	Prospective	AS, PsA, Pso, RA, SpA, Other	Yes	Switched to biosimilar	52	27 (14)	Adult	No primary endpoint specified	No info
Tweehuysen *et al.*, 2018[120]	Yes	No info	Netherlands	Hospital	Prospective	AS, PsA, RA	Yes	Switched to biosimilar	24	192 (75)	Adult	DAS28-CRP	No info
Vergara-Dangond *et al.*, 2017[152]	No	Yes	Spain	Hospital	Retrospective	AS, PsA, RA	Yes	Reference product versus switched to biosimilar	32	13 (2)	No info	DAS28	No info

** The number of total sample size is reported and if specified the number of RA-specific sample size is added in brackets.*

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.

7.2.2.4 Quality of evidence

Risk of bias assessment

Table 11 Risk of bias assessment

	PICO	Study name	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Yoo 2013[4]	1	PLANETRA	+	+	+	+	+	-	+
Yoo 2016[5]	1	PLANETRA	+	+	+	?	+	-	+
Cohen 2018[135]	1	REFLEC-TIONS	?	?	+	+	+	-	+
Alten 2019[134]	2	REFLEC-TIONS	?	?	+	?	+	-	+
Choe 2017[136]	1	EudraCT	+	+	+	+	+	+	+
Smolen 2017[137]	1	EudraCT	+	+	+	+	+	-	+
Smolen 2018[102]	2	EudraCT	+	+	+	+	+	+	+
Takeuchi 2015[138]	1	JapicCTI	+	+	+	?	-	?	+
Genovese 2020[139]	1	Genovese	?	?	?	?	?	+	+

+	Low risk of bias
?	Unclear risk of bias
-	High risk of bias

Random sequence generation was clearly described in six of nine publications (***Table 11***).[4,5,102,136,137,156] Six publications provided enough information to conclude that allocation concealment was adequately performed.[4,102,136–138,157] Participants and personnel were blinded in eight publications.[4,102,134–138,157] Adequate blinding of outcome assessment was reported in five publications.[4,102,135–137] One publication was identified with high risk of bias due to incomplete outcome data[138], one publication did not provide enough information[139]. For four of the five trials a study protocol was available to judge possible reporting bias.[4,135,136,139] In five publications, outcome reporting was not complete, because primary outcome parameters differed to the study protocol or secondary outcomes were not reported in the final publication,

resulting in a high risk of reporting bias.[4,5,134,135,137] Other risks of bias were not found. Finally, five of nine publications were judged as having a low risk of bias in at least 5 of 7 assessed domains.[4,5,102,136,137]

GRADE assessment

PICO 1

The certainty of evidence of effect for relevant outcomes for PICO 1 was rated from moderate to high (***Table 12***). According to the GRADE assessment, four of the five critical outcomes were rated as high and one as moderate. Of the five important outcomes, one was rated as high and four as moderate. The reason for the downgrading in each case was imprecision.

PICO 2

The certainty of evidence of effect for relevant outcomes for PICO 2 was rated from low to moderate (***Table 13***). According to the GRADE assessment, one critical outcome was rated as moderate and three as low. Both important outcomes were rated as low. The reasons for the downgrading were serious inconsistency in all outcomes due to different follow-up timepoints. Furthermore, five of the six outcomes presented serious imprecision due to wide 95% CI.

Table 12 GRADE assessment PICO 1

Question: Infliximab biosimilar compared to Infliximab reference product for rheumatoid arthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab biosimilar	Infliximab reference product	Relative (95% CI)	Absolute (95% CI)		
ACR20 (follow up: 30 weeks)												
4	randomised trials	not serious	not serious	not serious	not serious	none	624/966 (64.6%)	632/974 (64.9%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1.000** (from 45 fewer to 45 more)	⊕⊕⊕⊕ HIGH	CRITICAL
ACR50 (follow up: 30 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	236/642 (36.8%)	237/648 (36.6%)	**RR 1.01** (0.87 to 1.16)	**4 more per 1.000** (from 48 fewer to 59 more)	⊕⊕⊕⊕ HIGH	CRITICAL
ACR70 (follow up: 30 weeks)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	118/642 (18.4%)	116/648 (17.9%)	**RR 1.03** (0.82 to 1.30)	**5 more per 1.000** (from 32 fewer to 54 more)	⊕⊕⊕◯ MODERATE	CRITICAL
HAQ-DI Change from baseline (follow up: 30 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	642	648	-	MD **0.05 lower** (0.12 lower to 0.01 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment-emergent AE (follow up: 30 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	534/915 (58.4%)	531/923 (57.5%)	**RR 1.01** (0.94 to 1.09)	**6 more per 1.000** (from 35 fewer to 52 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab biosimilar	Infliximab reference product	Relative (95% CI)	Absolute (95% CI)		
SDAI Change from baseline (follow up: 30 weeks)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	642	648	-	MD **0.68 lower** (2.21 lower to 0.84 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
CDAI Change from baseline (follow up: 30 weeks)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	642	648	-	MD **0.91 lower** (2.38 lower to 0.56 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
EULAR moderate or good response (follow up: 30 weeks)												
3	randomised trials	not serious	not serious	not serious	not serious	none	457/916 (49.9%)	479/923 (51.9%)	**RR 0.96** (0.86 to 1.08)	**21 fewer per 1.000** (from 73 fewer to 42 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
DAS28-CRP remission (follow up: 30 weeks)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	Number of patients: Biosimilar n=626; Reference product: n=630 In summary, no relevant differences were found for the outcome "Patients in remission according to the DAS28-CRP" between biosimilar and reference product groups.				⊕⊕⊕◯ MODERATE	IMPORTANT
Treatment-emergent serious AE (follow up: 30 weeks)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	Number of patients: Biosimilar n=625; Reference product: n=630 In summary, no relevant differences were found for the outcome treatment-emergent serious AE between biosimilar and reference product groups.				⊕⊕⊕◯ MODERATE	IMPORTANT

*Please **see Table 2** for further information regarding the outcome instrument. **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **AE**: Adverse event*

a. wide 95%-CI includes both similarity and divergences between reference product and biosimilar

Table 13 GRADE assessment PICO 2

Question: Switched to biosimilar compared to continued reference product for rheumatoid arthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**switched to biosimilar**	**continued reference product**	**Relative (95% CI)**	**Absolute (95% CI)**		
ACR20 (follow up: range 54 weeks to 78 weeks)												
2	randomised trials	not serious	serious [a]	not serious	not serious	none	Number of patients: Switched to biosimilar n=237; Continued reference product: n=244 In summary, no relevant differences were found for the outcome ACR20 between switching to biosimilar and continuing reference product.				⊕⊕⊕◯ MODERATE	CRITICAL
ACR50 (follow up: range 54 weeks to 78 weeks)												
2	randomised trials	not serious	serious [a]	not serious	serious [b]	none	Number of patients: Switched to biosimilar n=237; Continued reference product: n=244 In summary, no relevant differences were found for the outcome ACR50 between switching to biosimilar and continuing reference product.				⊕⊕◯◯ LOW	CRITICAL
ACR70 (follow up: range 54 weeks to 78 weeks)												
2	randomised trials	not serious	serious [a]	not serious	serious [b]	none	Number of patients: Switched to biosimilar n=237; Continued reference product: n=244 In summary, no relevant differences were found for the outcome ACR70 between switching to biosimilar and continuing reference product.				⊕⊕◯◯ LOW	CRITICAL
Treatment emergent AE (follow up: 24 weeks)												
2	randomised trials	not serious	serious [c]	not serious	serious [b]	none	Number of patients: Switched to biosimilar n=237; Continued reference product: n=244 In summary, no relevant differences were found for the outcome treatment emergent AE between switching to biosimilar and continuing reference product.				⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**switched to biosimilar**	**continued reference product**	**Relative (95% CI)**	**Absolute (95% CI)**		
EULAR moderate or good response (follow up: range 54 weeks to 78 weeks)												
2	randomised trials	not serious	serious [a]	not serious	serious [b]	none	Number of patients: Switched to biosimilar n=237; Continued reference product: n=244 In summary, no relevant differences were found for the outcome EULAR response between switching to biosimilar and continuing reference product.				⊕⊕◯◯ LOW	IMPORTANT
Treatment emergent serious AE (follow up: 24 weeks)												
2	randomised trials	not serious	serious [a]	not serious	serious [b]	none	Number of patients: Switched to biosimilar n=237; Continued reference product: n=244 In summary, no relevant differences were found for the outcome treatment emergent serious AE between switching to biosimilar and continuing reference product.				⊕⊕◯◯ LOW	IMPORTANT

*Please **see Table 2** for further information regarding the outcome instrument.*

***CI:** Confidence interval; **RR:** Risk ratio; **AE**: Adverse event*

a. different follow up timepoints

b. wide 95% CI includes both similarity and divergences between reference product and biosimilar

c. different follow up timepoints (30-54 weeks and 54-78 weeks)

7.2.3 Findings efficacy

PICO 1

ACR20 – critical outcome

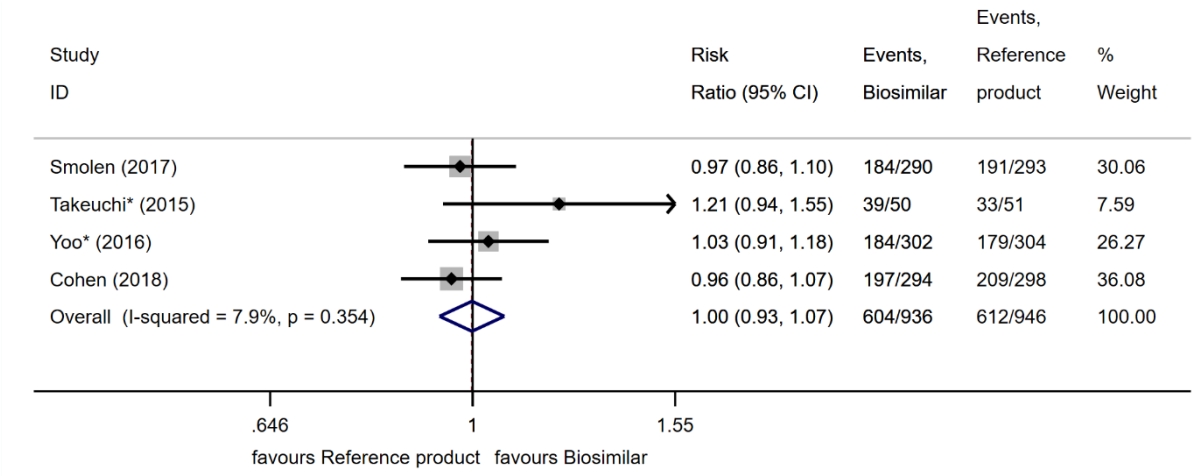
Seven studies reporting on five RCTs analysed treatment initiation with biosimilar compared to reference product. Follow-up timepoints were 22, 30 and 54 weeks.

ACR20 was reported in one study at the 22 weeks follow-up [139], in four studies at the 30 weeks and in three studies at the 54 weeks follow-up. The proportion of patients who achieved an ACR20 response rate was similar in the reference product group compared to the biosimilar group at all follow-up time points. At the 30 weeks follow-up, the meta-analysis yields a risk ratio (RR) of 1.00 (p = 0.354, 95%CI: 0.93 – 1.07, ***Figure 3*** a)) with low heterogeneity (I^2 = 7.9%). The similarity in ACR20 value did not differ when calculating risk ratio or odds ratio (***Figure 3*** b)). A description of the findings at the 54 weeks follow-up is provided in the ***Appendix 13.6.2***, ***Table A 1***.

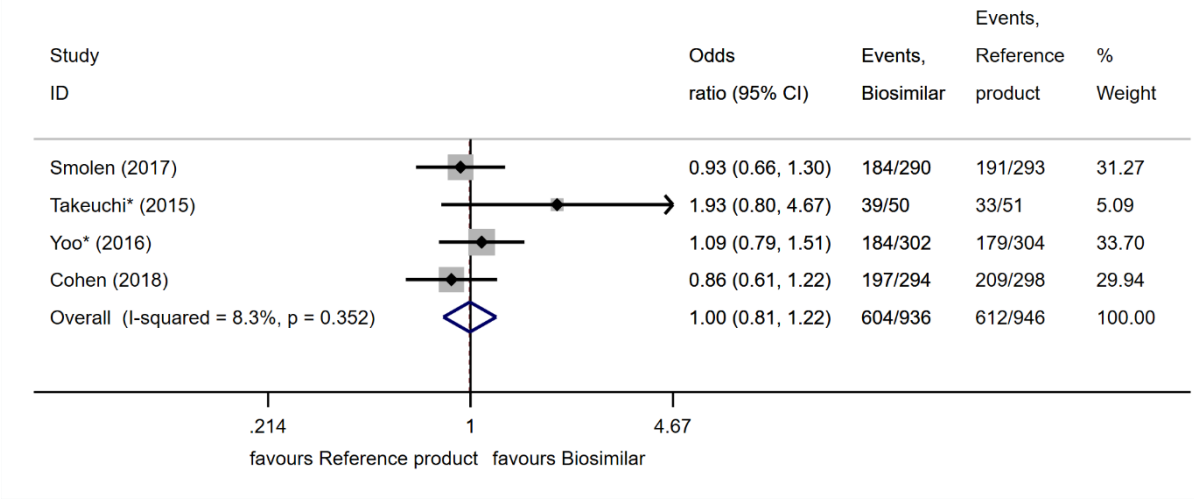
The certainty of evidence for the outcome ACR20 was judged as high (no downgrading).

Figure 3 Forest-plot of ACR20 after 30 weeks of treatment with reference product compared to biosimilar

a) Risk ratios



b) Odds ratios



*The figure presents a) risk ratios and b) odds ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant. * Studies investigated biosimilars approved in Switzerland*

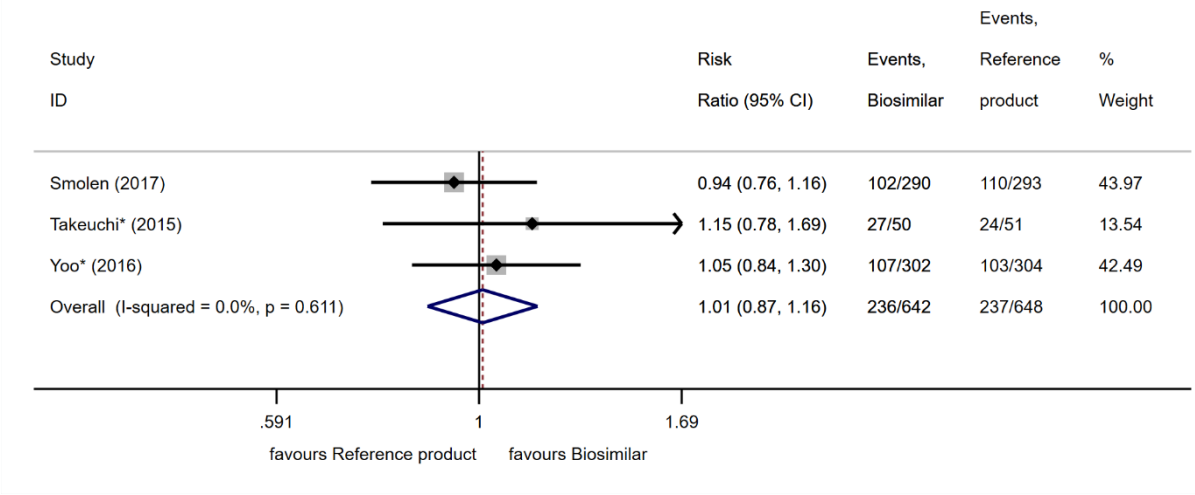
ACR50 and ACR70 – critical outcomes

Three studies reported on the ACR50 and ACR70 at the 30 weeks and 54 weeks follow-up. They showed similar results for the ACR50 and ACR70 for both groups. The RR for ACR50 was 1.01 (p = 0.611, 95%CI: 0.87 – 1.16, ***Figure 4***) and for ACR70 1.03 (p = 0.822, 95%CI: 0.82 – 1.30, ***Figure 5***) at the 30 weeks follow-up. The equivalent OR are presented in ***Appendix 13.6.1***, ***Figure A 6*** and ***Figure A 7*** and the results at the 54 weeks follow-up in ***Appendix 13.6.2***, ***Table A 1***. Heterogeneity was 0% for both outcomes.

The certainty of evidence for the outcome ACR50 was judged as high (no downgrading).

The certainty of evidence for the outcome ACR70 was judged as moderate. It was downgraded by one level because of serious imprecision.

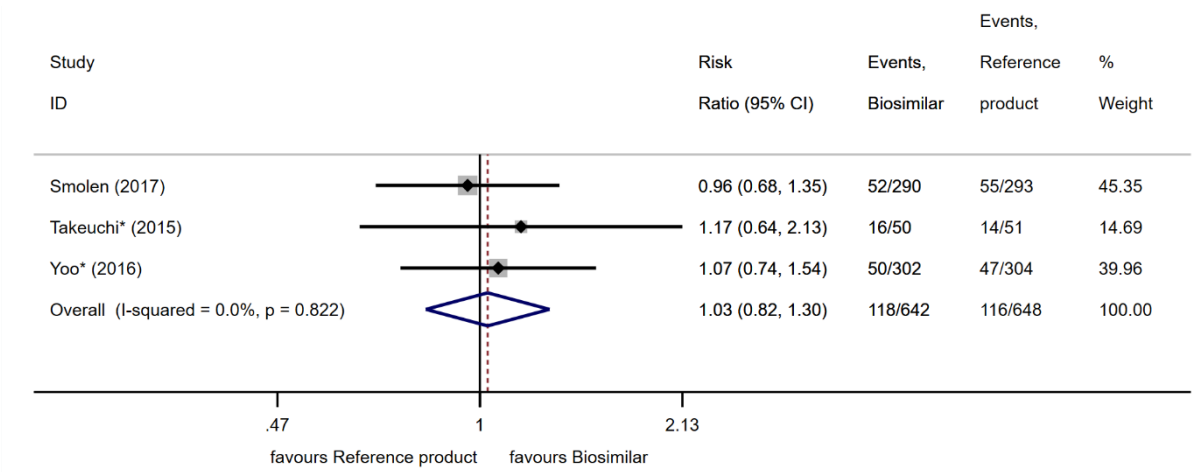
Figure 4 Forest-plot of ACR50 after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland*

Figure 5 Forest-plot of ACR70 after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

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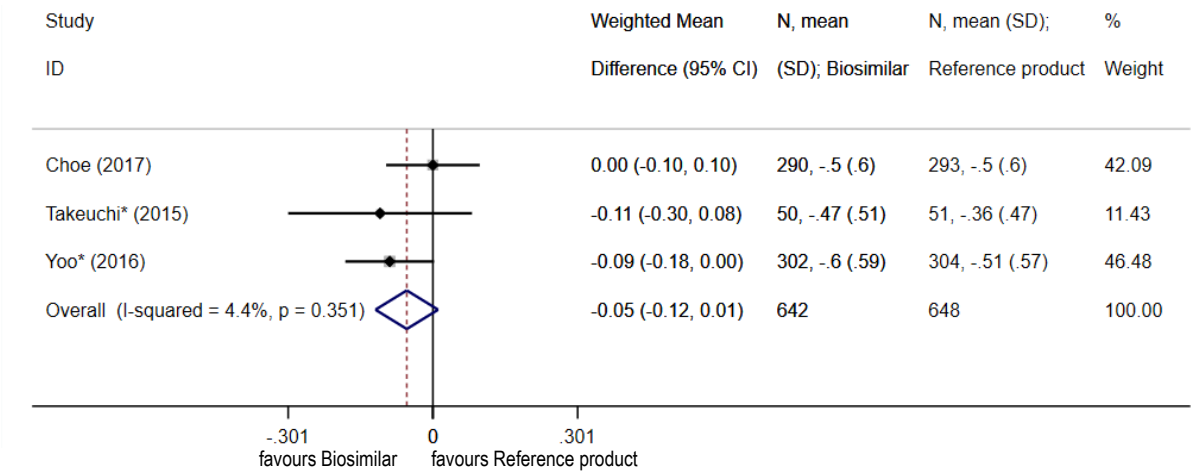
HAQ-DI – critical outcome

HAQ-DI change from baseline was reported in four studies at the 30 and 54 weeks follow-up. Details of uncertainty was missing in one and two studies at the 30 and 54 weeks follow-up, respectively. No difference was found between the two groups. At the 30 weeks follow-up, the weighted mean difference was -0.05 (p = 0.351, 95%CI: -0.12 – 0.01, I^2 = 4.4%, ***Figure 6***). The HAQ-DI change from baseline at the 54 weeks follow-up are provided in the ***Appendix 13.6.2***, ***Table A 1***.

The certainty of evidence for the outcome HAQ-DI was judged as high (no downgrading).

Figure 6 Forest-plot of HAQ-DI after 30 weeks of treatment with reference product compared to biosimilar



The figure presents weighted mean differences and its 95% confidence interval (95% CI) between treatments. If CI contains the value 0 the difference between treatments is not statistically significant.

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Publication bias of critical outcomes

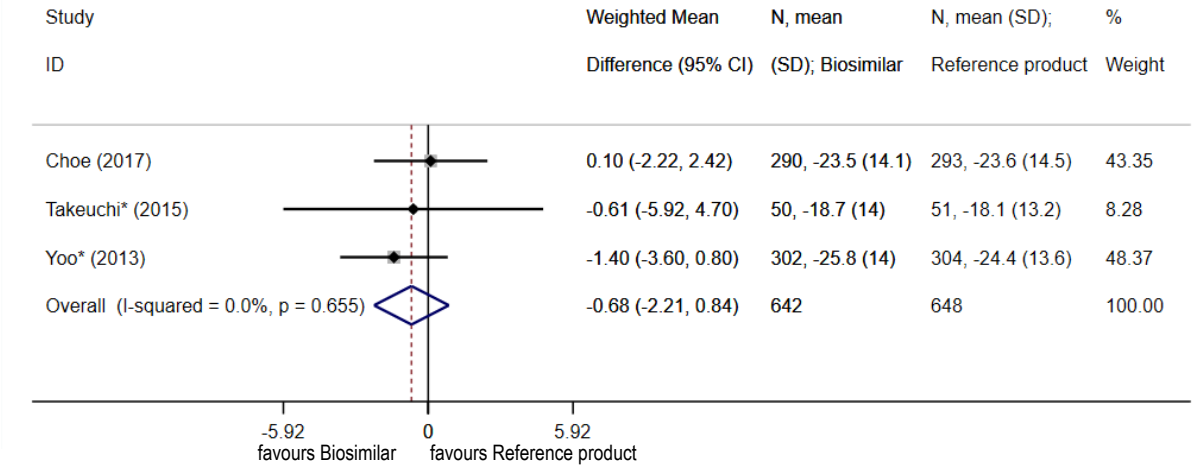
Publication bias for ACR20, ACR50, ACR70 and HAQ-DI was determined analysing the funnel plot (***Appendix 13.5***, ***Figure A 1*** - ***Figure A 5***). Visual inspection of the funnel-plot showed some aspect of asymmetry. However, as small studies with small, non-significant effect favouring reference product may be missing, this was not interpreted as suspicious, especially because the number of studies was very small.

SDAI – important outcome

Three studies presented data of SDAI change from baseline at 30 weeks and two at 54 weeks. No difference was found between the two investigated groups. The weighted mean difference of SDAI change from baseline at the 30 weeks follow-up was -0.68 (p = 0.655, 95%CI: -2.21 – 0.84, ***Figure 7***) with low heterogeneity (I^2 = 0%). The SDAI change from baseline at the 54 weeks follow-up are provided in the ***Appendix 13.6.2***, ***Table A 1***.

The certainty of evidence for the outcome SDAI was judged as moderate. It was downgraded by one level because of serious imprecision.

Figure 7 Forest-plot of SDAI after 30 weeks of treatment with reference product compared to biosimilar



The figure presents weighted mean differences and its 95% confidence interval (95% CI) between treatments. If CI contains the value 0 the difference between treatments is not statistically significant.

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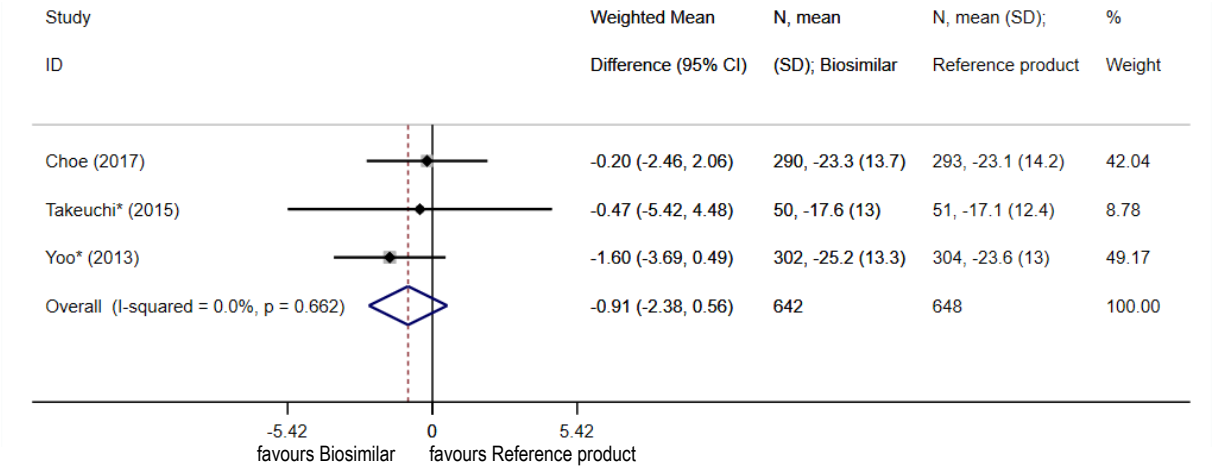
CDAI – important outcome

Three studies presented data of CDAI change from baseline at 30 weeks and two at 54 weeks. No difference was found between the two investigated groups. The weighted mean difference of CDAI change from baseline at the 30 weeks follow-up was -0.91 (p = 0.662, 95%CI: -2.38 – 0.56, ***Figure 8***) with low heterogeneity (I^2 = 0%). The CDAI change from baseline at the 54 weeks follow-up are provided in the ***Appendix 13.6.2***, ***Table A 1***.

The certainty of evidence for the outcome CDAI was judged as moderate. It was downgraded by one level because of serious imprecision.

Figure 8 Forest-plot of CDAI after 30 weeks of treatment with reference product compared to biosimilar



The figure presents weighted mean differences and its 95% confidence interval (95% CI) between treatments. If CI contains the value 0 the difference between treatments is not statistically significant.

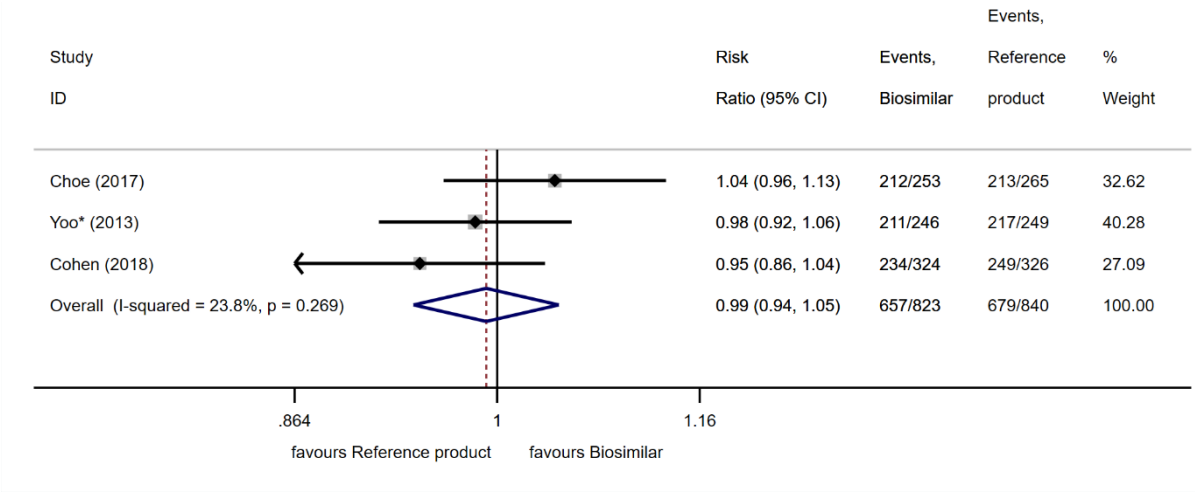
** Studies investigated biosimilars approved in Switzerland*

EULAR response – important outcome

Three studies presented data of patients achieving a moderate or good EULAR response at 30 weeks and two at 54 weeks. No difference was found between the two investigated groups. The risk ratio moderate/good EULAR response at the 30 weeks follow-up was 0.99 (p = 0.269, 95%CI: 0.94 – 1.05, ***Figure 9***) with low heterogeneity (I^2 = 23.8%). The equivalent OR are presented in ***Appendix 13.6.1***, ***Figure A 9*** and the results at the 54 weeks follow-up in ***Appendix 13.6.2***, ***Table A 1***.

The certainty of evidence for the outcome EULAR response was judged as high (no downgrading).

Figure 9 Forest-plot of moderate/good EULAR response after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

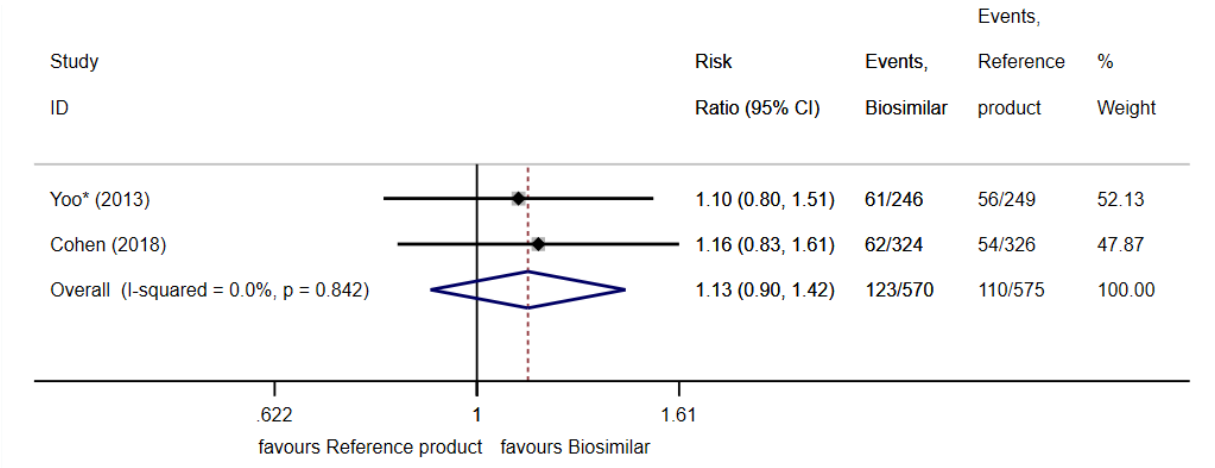
** Studies investigated biosimilars approved in Switzerland*

DAS28 remission – important outcome

One study presented data of DAS28-ESR remission at 30 weeks, one at 54 weeks, two studies presented data of DAS28-CRP remission at the 30 weeks follow-up and one at the 54 weeks follow-up. None of them found a difference between the two investigated groups. The RR of DAS28-CRP remission at the 30 weeks follow-up was 1.13 (p = 0.842, 95%CI: 0.90 – 1.42, ***Figure 10***) with low heterogeneity (I^2 = 0%). The OR is presented in ***Appendix 13.6.1***, ***Figure A 8***.

The certainty of evidence for the outcome DAS28-CRP remission was judged as moderate. It was downgraded by one level because of serious imprecision.

Figure 10 Forest-plot of DAS28-CRP remission after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

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Further outcomes

The results of the further outcome parameters documenting clinical efficacy (DAS28-CRP Change from baseline, DAS28-ESR Change from baseline), immunogenicity (ADAb, NAb), PK/PD (C min/trough, acute phase reactant, C max, T max, PTF, C avg) and PROM (patient global assessment, physician global assessment, pain) are summarized in the following tables (***Table 14- Table 17***). All studies found similar results for each outcome parameter in the group treated with the reference product compared to the biosimilar.

Table 14 Clinical efficacy PICO 1

Study	-	0	+	Follow-up	Reference product	Biosimilar
DAS28-CRP Score (Change from baseline ± standard deviation [where specified])						
Yoo* 2016		X		30	-2.1	-2.3
Cohen 2018		X		30	-2.1	-2.1
Takeuchi* 2015		X		30	-1.955 ± 1.331	-2.08 ± 1.456
Genovese 2020		X		22	-2.06	-2.06
DAS28-ESR Score (Change from baseline ± standard deviation)						
Yoo* 2016		X		30	-2.3	-2.5
Choe 2017		X		30	-2.3 ± 1.5	-2.3 ± 1.4
Takeuchi* 2015		X		30	-1.961 ± 1.326	-2.142 ± 1.471

-: favours reference product, 0: no difference, +: favours biosimilar

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Table 15 Immunogenicity PICO 1

Study	-	0	+	Follow-up	Reference product	Biosimilar
ADAb (Patients having anti-drug antibodies)						
Cohen 2018		X		30	44.17%	42.11%
Choe 2017		X		0-30†	49.66%	55.05%
Yoo* 2013		X		30	48.20%	48.40%
Genovese 2020		X		22	60.61%	57.09%
NAb (Patients having neutralising antibodies among all patients with positive ADA result)						
Cohen 2018		X		30	83.33%	77.21%
Genovese 2020		X		22	34.38%	31.54%

-: favours reference product, 0: no difference, +: favours biosimilar

† at least one positive ADA result up to week 30

** Studies investigated biosimilars approved in Switzerland*

Table 16 PK/PD PICO 1

Study	-	0	+	Follow-up	Reference product	Biosimilar
C min/trough [µg/mL]						
Cohen 2018		X		14	1.025 (95%CI: 0–7.643)	1.497 (95%CI: 0–10.590)
Choe 2017		X		14	3.38 (SD: 3.65)	3.593 (SD: 6.09)
Yoo* 2013		X		14	1.07 (CV: 140)	1.05 (CV: 136)
Takeuchi* 2015		X		14	2.31 (SD: 1.90)	2.68 (SD: 2.44)
Genovese 2020		X		22	1.1844 (Geometric CV: 3.2794)	1.1270 (Geometric CV: 2.9155)
C max [µg/mL]						
Cohen 2018		X		14	68.45 (95%CI: 3.37–144.50)	71.25 (95%CI: 1.62–150.50)
Yoo* 2013		X		14	85.25 (CV: 40)	90.25 (CV: 36)
Takeuchi* 2015		X		14	115 (SD: 41.4)	113 (SD: 35.9)
Acute phase reactant CRP (Change from baseline± standard deviation)						
Yoo* 2016		X		54	-0.66 ± 2.66	-0.67 ± 2.17
Choe 2017		X		30	-5.2 ± 19.9	-3.7 ± 21.6
Acute phase reactant ESR (Change from baseline± standard deviation)						
Yoo* 2016		X		54	-15.2 ± 21.89	-12.3 ± 22.13
Choe 2017		X		30	-15.5 ± 22.7	-15.4 ± 19.8

-: favours reference product, 0: no difference, +: favours biosimilar

SD = standard deviation, CI = confidence interval, CV = coefficient of variation

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Table 17 Patient reported outcome measurements (PROM) PICO 1

Study	-	0	+	Follow-up	Reference product	Biosimilar
Patient global assessment [100mm VAS] (Change from baseline ± standard deviation)						
Choe 2017		X		30	-25.2 ± 26.1	-23.8 ± 23.9
Yoo* 2013		X		30	-27 ± 25.6	-28.1 ± 25.9
Physician global assessment [100mm VAS] (Change from baseline ± standard deviation)						
Choe 2017		X		30	-32.8 ± 22.2	-32.7 ± 20.7
Yoo* 2013		X		30	-35.3 ± 21.2	-35.6 ± 20.6
Pain [100mm VAS] (Change from baseline ± standard deviation)						
Choe 2017		X		30	-25.9 ± 27.2	-21.9 ± 24.0
Yoo* 2013		X		30	-27.8 ± 24.9	-29.5 ± 25.5

-: favours reference product, 0: no difference, +: favours biosimilar

*VAS = visual analogue scale; * Studies investigated biosimilars approved in Switzerland*

PICO 2

Two studies analysed switching from reference product to biosimilar compared to the continuation of reference product treatment (PICO 2).[102,134]

Both studies analysed a time period of 24 weeks after switch. However, one from 30 to 54 weeks and one from 54 to 78 weeks after treatment initiation. Due to this difference, no meta-analysis was conducted and outcomes for PICO 2 were summarized in a descriptive manner.

In none of the outcomes, differences between the reference product and the biosimilar were statistically significant or clinically relevant (***Table 18 - Table 20***).

The certainty of evidence for the critical outcomes was judged as low (ACR50, ACR70) to moderate (ACR20). The important outcome (EULAR response) was judged as low. Downgrading occurred because of serious inconsistency (for all outcomes) and serious imprecision (for ACR50, ACR70 and EULAR response).

Table 18 Clinical efficacy PICO 2

Study	-	0	+	Follow-up	Continued reference product	Switch to biosimilar
ACR20 (Proportion of patients who achieved an ACR20 response rate)						
Smolen 2018		X		78	68.80%	63.50%
Alten 2019		X		54	64.34%	70.63%
ACR50 (Proportion of patients who achieved an ACR50 response rate)						
Smolen 2018		X		78	47.30%	37.60%
Alten 2019		X		54	42.66%	45.45%
ACR70 (Proportion of patients who achieved an ACR70 response rate)						
Smolen 2018		X		78	31.20%	22.40%
Alten 2019		X		54	23.08%	24.48%
DAS28-CRP (a) Change from baseline, b) Patients in remission)						
Alten 2019		X		30-54	a) -0.2	a) -0.2
Alten 2019		X		54	b) 23.08%	b) 20.28%
HAQ-DI (Change from baseline)						
Alten 2019		X		30-54	0.02	-0.04
EULAR response (Patients achieving moderate or good response)						
Smolen 2018		X		78	84.95%	84.71%
Alten 2019		X		54	76.22%	78.32%

-: favours reference product, 0: no difference, +: favours biosimilar

Table 19 Immunogenicity PICO 2

Study	-	0	+	Follow-up	Continued reference product	Switch to biosimilar
ADAb (Patients having at least one positive ADA result during the transition extension period among all patients regardless of prior ADA result)						
Smolen 2018		X		54-78	50.50%	45.74%
Alten 2019		X		30-54	60.1%	58.0%
NAb (Patients with NAbs among all patients with positive ADA result during the transition period)						
Smolen 2018		X		78	71.40%	33.30%
Alten 2019		X		54	84.9%	78.3%

-: favours reference product, 0: no difference, +: favours biosimilar

Table 20 PD/PK PICO 2

Study	**-**	**0**	**+**	**Follow-up**	**Continued reference product**	**Switch to biosimilar**
Acute phase reactant CRP (Change from baseline)						
Alten 2019		X		0-54	-6.9	-15.2

-: favours reference product, 0: no difference, +: favours biosimilar

7.2.4 Findings effectiveness

The extent to which infliximab biosimilars produce equivalent results to the infliximab reference product under non-research conditions for patients with RA (i.e. fulfilling conditions for effectiveness) is difficult to estimate. However, the HTA authors judged the included RCTs as fulfilling at least some features of real-world non-research conditions. Therefore, RWE studies were only used to investigate therapy duration/discontinuation and nocebo effects, two aspects especially relevant for PICO 2.

The systematic literature search identified 17 RWE studies (***Table 21***).

Therapy duration: Ten of 17 studies reported on drug retention. Discontinuation of infliximab biosimilar ranged from 14 to 31% in the first year. Four studies reported on discontinuation rates separately for biosimilar and reference product. Three studies found higher discontinuation rates for the biosimilar[140,143,150], one for the reference product[148].

Nocebo effect: Two studies reported on the nocebo effect.[140,151] One study presented 12.8% nocebo response and one study 4 to 7%.

Table 21 Therapy duration and nocebo effects reported in RWE studies

First author, year	Switch	Therapy duration	Nocebo effect
Avouac *et al.*, 2018[141]	Yes	Drug retention: 85% at the time of the third infusion; 77% at the last study visit (mean 34 weeks)	Not reported
Boone *et al.*, 2018[140]	Yes	Discontinuation: 15% per year in the first year. 3.4% lower rate in drug retention for patients with infliximab biosimilar compared to infliximab reference product	An overall nocebo response of 12.8% was found among the patients during a minimal observation period of 6 months after the transition to biosimilar infliximab
Dutcher et al., 2020[153]	No	Not reported	Not reported
Fisher et al., 2020[154]	No	Not reported	Not reported
Glintborg *et al.*, 2018[142]	Yes	Not reported	Not reported
Glintborg *et al.*, 2017[143]	Yes	Drug retention: Biosimilar (1year) 84.1% (95%CI 81.3 to 86.5); reference product 86.2% (95%CI 84.0 to 88.0) (Adjusted absolute retention rate: 83.4 (95% CI 80.8 to 86.2) and 86.8% (95% CI 84.8 to 88.8))	Not reported
Grøn *et al.*, 2019[144]	No	Drug retention: 69% for infliximab biosimilar after 1 year	Not reported
Holroyd *et al.*, 2018[145]	Yes	Drug retention: 86% at 1-year follow-up	Not reported
Layegh *et al.*, 2019[146]	Yes	Drug retention: 87% continued with infliximab biosimilar at 2-year follow-up	Not reported
Nikiphorou *et al.*, 2019[148]	Yes	Discontinuation: 18% infliximab reference product; 5% infliximab biosimilar due to inefficacy. Total: 62% Infliximab reference, 30% Biosimilar in the first 2 years of treatment	Not reported
Nikiphorou *et al.*, 2015[147]	Yes	Discontinuation: 28.2% 11 months (median)	Not reported

First author, year	Switch	Therapy duration	Nocebo effect
Saxby et al., 2020[155]	Yes	Not reported	Not reported
Scavone *et al.*, 2018[149]	No	Not reported	Not reported
Scherlinger *et al.*, 2018[150]	Yes	Drug retention: 72% (with biosimilar) after a median follow-up of 33 weeks, 88% (with reference product) after 1 year	Not reported
Schmitz *et al.*, 2017[151]	Yes	Discontinuation: 26% in the first year after switching to infliximab biosimilar	"All switch studies we found reported that dis-continuation of biosimilar therapy was partly due to subjective reasons, which could be due to the "nocebo effect" (disease worsening due to negative expectations). In our study, this was probably the case for one or two [of 27 included] patients."
Tweehuysen *et al.*, 2018[120]	Yes	Not reported	Not reported
Vergara-Dangond *et al.*, 2017[152]	Yes	Not reported	Not reported

7.2.5 Findings safety

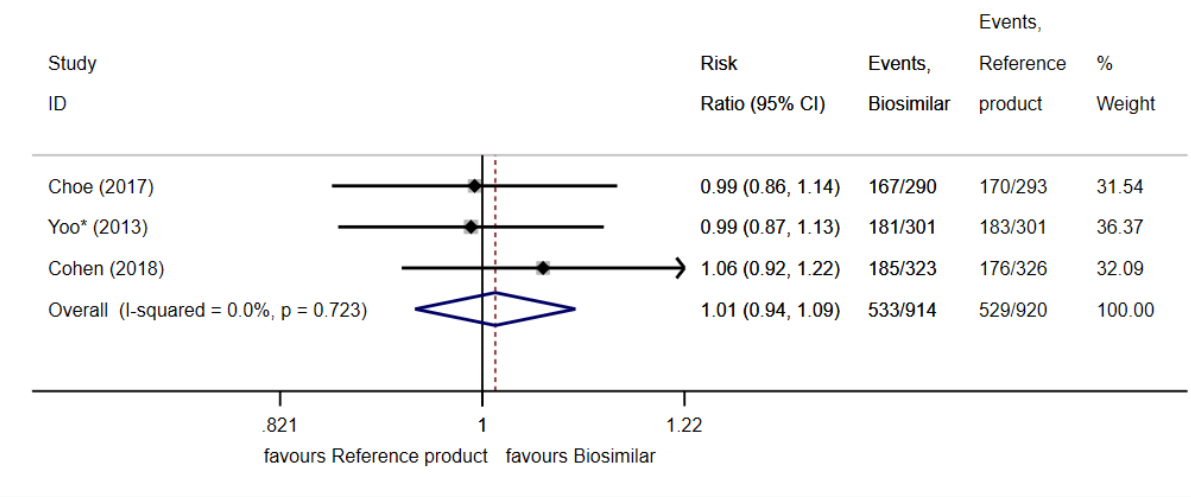
PICO 1

Treatment-emergent adverse events – critical outcome

Three studies reported on treatment emergent adverse events (TEAE) at the 30 weeks follow-up for PICO 1 and two at the 54 weeks follow-up. The proportion of patients who had experienced at least one TEAE was similar in the biosimilar and reference product group. At the 30 weeks follow-up RR was 1.01 (p = 0.723, 95%CI: 0.94-1.09, ***Figure 11***, ***Appendix 13.6.1***, ***Figure A 10*** for odds ratios). Heterogeneity was very low with 0%. A description of the findings at the 54 weeks follow-up is provided in the ***Appendix 13.6.3***, ***Table A 2***.

The certainty of evidence for the outcome TEAE was judged as high (no downgrading).

Figure 11 Treatment emergent adverse events during 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland*

Publication bias of critical outcome

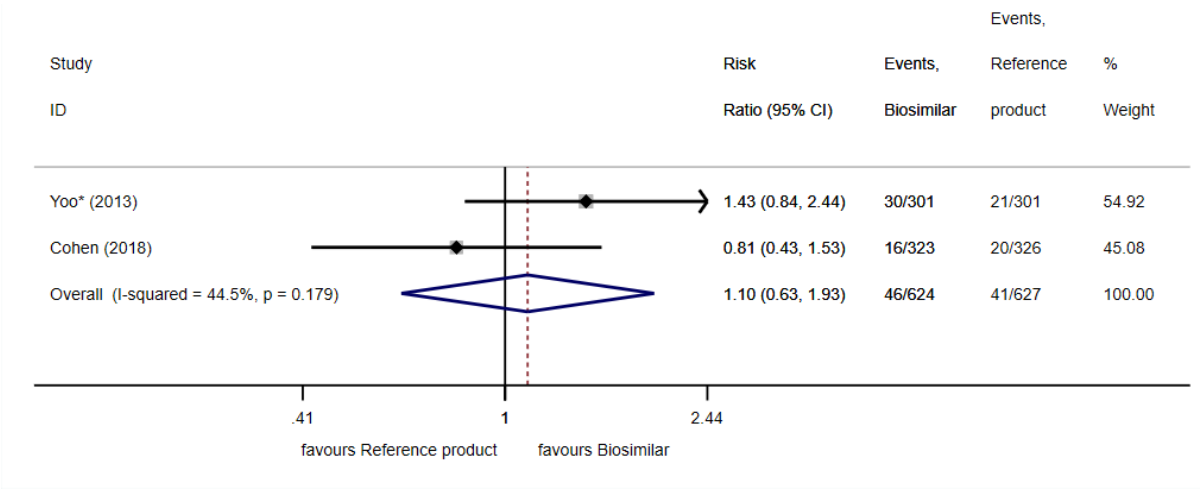
Publication bias for TEAE was determined analysing the funnel plot (***Appendix 13.5***, ***Figure A 5***). Visual inspection of the funnel-plot showed no noticeable aspect of asymmetry. However, it is difficult to make a sound statement since the number of studies was very small.

Treatment-emergent serious adverse events – important outcome

Two studies reported on treatment emergent serious adverse events (TESAE) at the 30 weeks follow-up for PICO 1 and two at the 54 weeks follow-up. The proportion of patients who had experienced at least one TESAE was similar in the biosimilar and reference product group. At the 30 weeks follow-up, RR was 1.10 (p = 0.179, 95%CI: 0.63 – 1.93, ***Figure 12***, ***Appendix 13.6.1***, ***Figure A 11*** for odds ratios). Heterogeneity was moderate with 44.5%. A description of the findings at the 54 weeks follow-up is provided in the ***Appendix 13.6.3***, ***Table A 2***.

The certainty of evidence for the outcome TESAE was judged as moderate. It was downgraded by one level because of serious imprecision.

Figure 12 Treatment emergent serious adverse events during 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland*

Results of adverse events, serious adverse events and discontinuations due to treatment-emergent adverse events for PICO 1 showed no clinically meaningful difference between patient groups treated with the reference product compared to the biosimilar (***Table 22***).

Table 22 Adverse events PICO 1

Study	-	0	+	Follow-up	Reference product	Biosimilar
Adverse events (Percentage of patients with at least one event)						
Genovese 2020		X		22	49.64%	51.80%
Takeuchi* 2015		X		54	86.79%	88.24%
Serious adverse events (Percentage of patients with at least one event)						
Genovese 2020		X		22	5.04%	3.24%
Choe 2017		X		30	8.87%	8.97%
Takeuchi* 2015		X		54	15.09%	15.69%
Treatment emergent adverse events leading to treatment discontinuation (Percentage of patients with at least one event)						
Genovese 2020		X		22	6.47%	5.76%
Cohen 2018		X		30	7.36%	7.12%
Takeuchi* 2015		X		54	11.32%	17.65%
Yoo* 2016		X		54	15.67%	10.93%

-: favours reference product, 0: no difference, +: favours biosimilar

** Studies investigated biosimilars approved in Switzerland*

PICO 2

Two studies reported on adverse events during the switching period from reference product to biosimilar compared with continuation of biosimilar. The period investigated was 24 weeks in both studies, one study initiated switching 30 weeks and one 54 weeks after treatment initiation. There was no statistically significant difference in adverse events between the group which switched to biosimilar compared to the group which stayed on the reference product (***Table 23***).

The certainty of evidence for the outcome TEAE and TESAE was judged as low. They were downgraded by two levels because of serious inconsistency and serious imprecision.

Table 23 Adverse Events PICO 2

Study	-	0	+	Follow-up	Continued reference product	Switched to biosimilar
Treatment emergent adverse events (Percentage of patients with at least one event)						
Smolen 2018		X		54-78	35.64%	36.17%
Alten 2019		X		30-54	33.57%	37.76%
Treatment emergent serious adverse events (Percentage of patients with at least one event)						
Smolen 2018		X		54-78	2.97%	6.38%
Alten 2019		X		30-54	7.69%	2.80%
Treatment emergent adverse events leading to discontinuation (Percentage of patients with at least one event)						
Alten 2019		X		30-54	6.99%	4.90%

-: favours reference product, 0: no difference, +: favours biosimilar

Summary statement efficacy, effectiveness and safety

Overall, 2499 RA patients were included in the analysis. Most RCTs were multinational. Two RCTs analysed biosimilars which are approved in Switzerland.

Five RCTs investigated the impact of treatment initiation with infliximab biosimilar compared to treatment initiation with infliximab reference product in patients with RA (PICO 1). All five RCTs showed equivalent clinical efficacy and safety between the two groups 22, 30 and 54 weeks after treatment initiation . The meta-analysis of the critical and important outcomes confirmed that there is no difference in outcomes between treatment initiation with biosimilar and reference product. The certainty of evidence for the critical and important outcomes was judged as moderate to high.

Two RCTs analysed switching from infliximab reference product to biosimilar compared to the continuation of reference product in patients with RA (PICO 2). Both studies did not find any differences in

outcomes between the analysed groups. However, the certainty of evidence for PICO 2 was judged as low to moderate. The reasons for the downgrading were serious inconsistency in all outcomes due to different follow-up timepoints. Furthermore, five of the six outcomes presented serious imprecision due to wide 95% CI. A wide 95% CI includes both, similarity and divergences between reference product and biosimilar.

No RCT analyzed switching from infliximab biosimilar to the reference product (PICO 3). Therefore, this research question could not be answered.

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8 Health economic analysis

To address the health economic research questions, we first searched and analysed available evidence. However, as the reviewed health economic evidence was not sufficient to answer the research questions, we developed a de novo cost-minimisation and budget impact model in a second step of the HTA.

8.1 Methodology literature review

8.1.1 Databases and search strategy

The search and study selection for health economic evidence was combined with the one for effectiveness, efficacy and safety. Details about data sources, search strategies, inclusion and exclusion criteria as well as study selection procedure are described in chapter 7.1.1.

8.1.2 Assessment of quality of evidence

The quality of the health economic evidence was assessed using the CHEC checklist.[158]

8.1.3 Data analysis

Data were summarized in a descriptive manner.

The outcomes of each study were exported into MS Excel by one researcher and verified by a second researcher. Inconsistencies were solved by consensus.

Therapy discontinuation and nocebo effects based on RWE studies were tabularized.

8.2 Results literature review

8.2.1 PRISMA flow diagram

The PRISMA flow diagram is presented in chapter 7.2.1.

8.2.2 Evidence table

With the initial systematic review, eleven health economic studies were identified as relevant for the scoping report.[142,159–168] The updated literature search for the HTA report rendered two additional that

fulfilled the full screening inclusion criteria.[169,170] Therefore, 13 studies were included in our analysis (***Table 24***).

CoI and funding: All thirteen studies reported on CoI, with seven studies reporting at least one author with a CoI. Study funding was reported for twelve 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 7.1.1.2***). Two studies estimated the budget impact for five countries.[164,165] Of the included studies, four were performed for the UK and three for Italy, France and the US, with the remainder for Belgium, Canada, Denmark, Germany, Netherlands and Spain. No study was identified for Switzerland in the searches.

Types of health economic studies: The study by Ghabri *et al.*[170] was the only full economic evaluation identified. Six studies were BIAs and five studies costing studies. Costing studies were mainly retrospective studies. One study reported on resource utilization without assigning unit costs.[171] Therefore, this study did not report an outcome in monetary units.

Perspective: Four studies were conducted from a healthcare system perspective. Six 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 in most studies and reaching 40 years in the full economic evaluation.

Indications: Four studies were conducted in a RA-only population. The remaining studies included several inflammatory or rheumatic diseases, in particular AS, AxSpA, Morbus Crohn, IBD, PsA, psoriasis, UC or rheumatic conditions in general without explicit reference to the conditions comprising this group. In these multi-disease studies, results were generally not reported per single disease.

Table 24 Study characteristics of included health economic studies

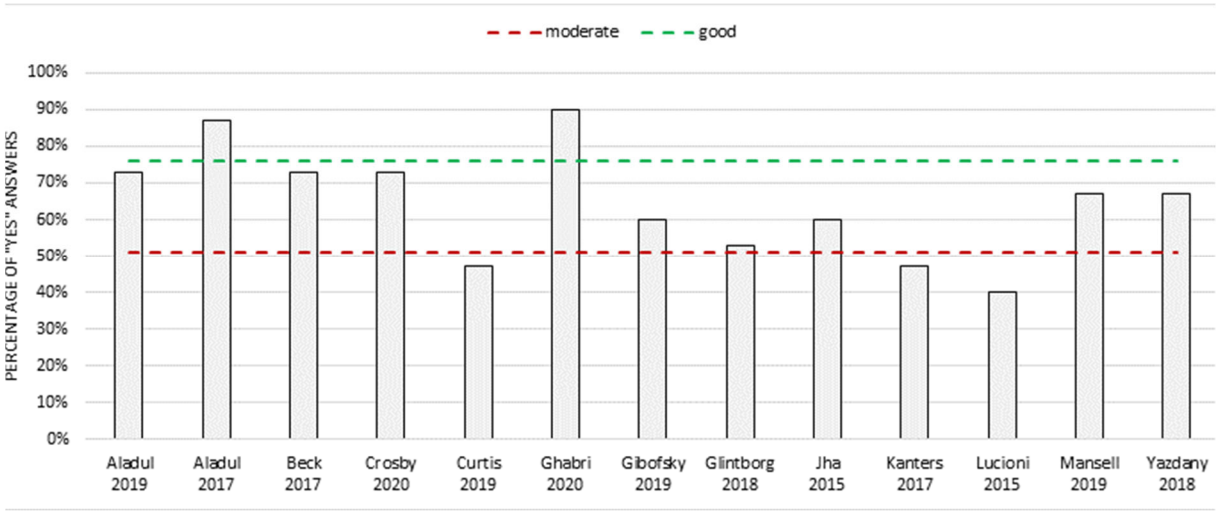
First author, year	CoI for at least one author	Industry funding	Countries	Full economic evaluation	Type of HE study	Perspective	Time horizon (years)	Indications	Subgroups
Aladul *et al.*, 2019[159]	No	No	United Kingdom	No	BIA	Healthcare system (NHS)	3	AS, Crohn, PsA, RA, UC	No info
Aladul *et al.*, 2017[160]	No	No	United Kingdom	No	Costing	Healthcare system (NHS)	3	AS, PsA, RA	No info
Beck *et al.*, 2017[161]	Yes	No info	France	No	BIA	Health insurance (CNAMTS)	1	RA	Alsace and France
Crosby *et al.*, 2020[169]	No	No	Canada	No	Costing	Healthcare payer	1	Rheumatic Conditions and Inflammatory Bowel Disease	Province
Curtis *et al.*, 2019[162]	Yes	No	United States	No	Costing	Healthcare insurance (Medicare)	1.5	RA	No info
Ghabri *et al.*, 2020[170]	No	No	France	Yes	CUA	Healthcare payer	40	RA	No info
Gibofsky *et al.*, 2019[163]	Yes	Yes	United States	No	BIA	Healthcare provider/payer	0.25	AS, Crohn, PsA, Pso, RA, UC	No info
Glintborg *et al.*, 2018[171]	Yes	Yes	Denmark	No	Resource use	Healthcare system	0.5	AxSpA, Pso, RA	No info
Jha *et al.*, 2015[164]	Yes	Yes	Belgium, Germany, Italy, Netherlands, United Kingdom	No	BIA	Healthcare payer	1	AS, Crohn, PsA, Pso, RA, UC	Country
Kanters *et al.*, 2017[165]	Yes	Yes	France, Germany, Italy, Spain, United Kingdom	No	BIA	Healthcare payer	5	AS, IBD, RA	Country
Lucioni *et al.*, 2015[166]	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[168]	No	Yes	Canada	No	Costing	Healthcare provider/payer	2	Not applicable	Province
Yazdany *et al.*, 2018[167]	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; CUA, Cost-Utility Analysis; IBD, Inflammatory Bowel Disease; OOP, Out-Of-Pocket; PsA, Psoriatic Arthritis; Pso, Psoriasis; RA, Rheumatoid Arthritis; UC, Ulcerative Colitis

8.2.3 Quality Assessment

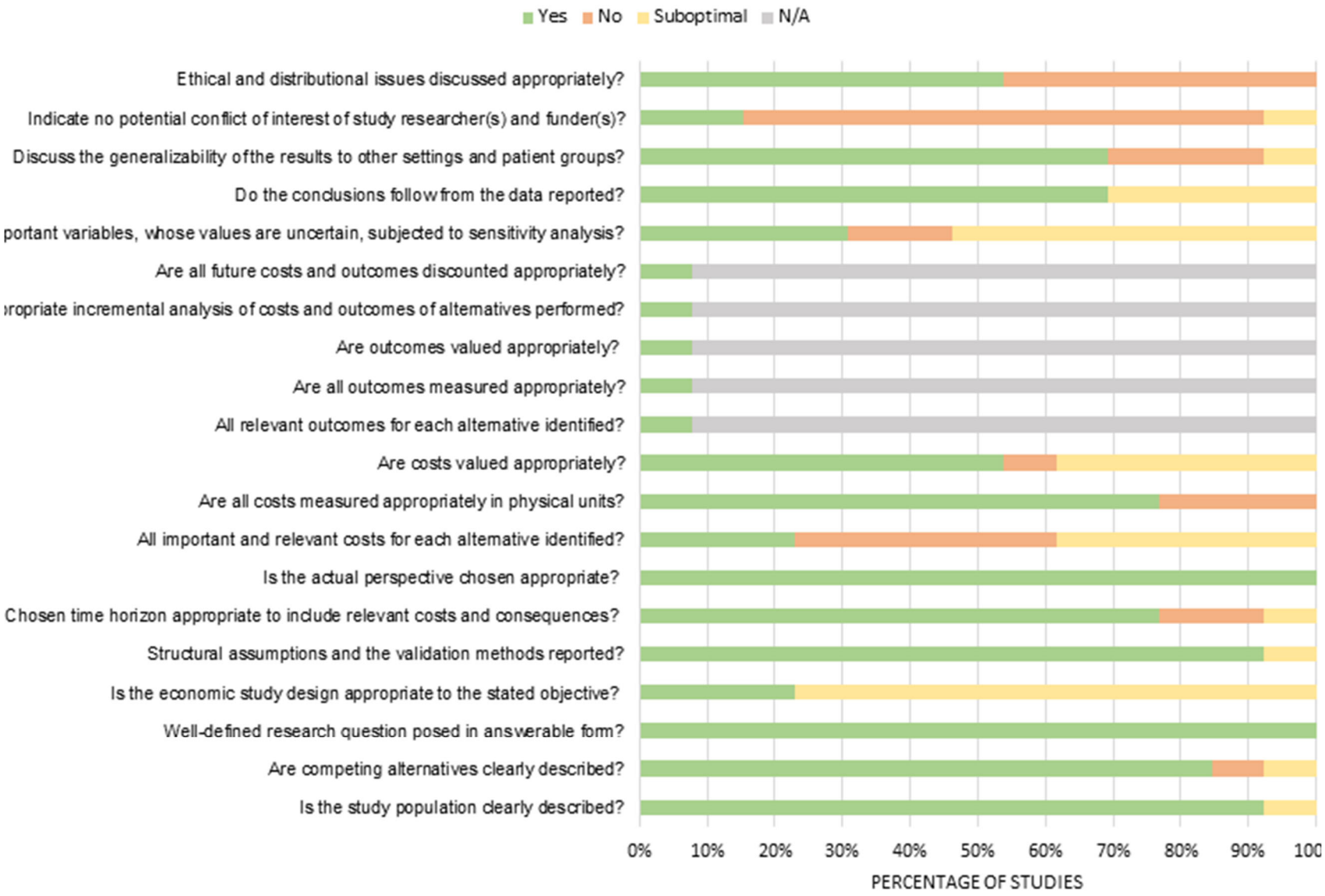
Figure 13 shows the quality of economic evidence per study and ***Figure 14*** per Consensus on Health Economic Criteria (CHEC) checklist item. Details per study are presented in the ***Appendix section 13.7***. ***Figure 13*** illustrates that using the methodology described by Sagili *et al.*[172] to derive the total quality score results in two out of the thirteen included articles falling below the moderate quality threshold and thus satisfy less than 50% of the criteria set by the CHEC checklist. As indicated in ***Figure 14***, there are questions that are not applicable to certain studies. The CHEC checklist was initially developed to examine full economic evaluations that compare interventions not only in terms of costs, but also outcomes, whereas in our review we identified only one full economic evaluation. To the best of our knowledge, there is currently no checklist designed to assess specifically the quality of budget impact analyses and costing studies.

Figure 13 Quality of economic evidence (CHEC)



The levels of evidence are based on the scoring system used by Sagili et al.[172], with low, moderate, good and excellent quality determined by cut-off values of ≤50, 51–75, 76–95 and >95 , respectively.

Figure 14 Overview of sources of bias and limitations (CHEC)



8.2.4 Findings from available health economic evidence

Drug cost: Eleven out of thirteen studies investigated drug costs. The two remaining studies investigated healthcare service resource use without assigning unit costs[171] and extra time spent by physicians as well as laboratory tests and other procedures required due to non-medical switching[163].

Total budget impact: Seven studies reported total budget impact. However, this outcome was estimated differently between studies. Four studies assumed that the main relevant difference would be due to drug costs. Two studies also included differences due to drug administration and monitoring[163,165] and one study also included direct non-medical costs based on transport expenses[161].

Resource use: Resource utilization was reported separately in three studies.[162,163,171]

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. Only one full health economic evaluation was identified.[170] 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. While one study reported considerable short-term switching costs due to increased drug administration and monitoring[163], another study found only marginal changes with no clinically relevant increase in resource use after switching[171].

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 compared to infliximab biosimilar in the treatment of RA, for Switzerland directly. Furthermore, the methodological heterogeneity between the included HE studies in terms of health conditions, countries, evaluation approaches, sources of costs, time horizon, RA incidence rate, reference product market share and other assumptions impede to draw any conclusions for Switzerland. Therefore, we decided to build a de novo health economic model.

8.3 Methodology de novo health economic model

8.3.1 Overview

The reviewed health economic evidence is not sufficient to address the posed research questions, on either cost-effectiveness or budget impact of the infliximab reference product compared to infliximab biosimilar in the treatment of RA, for Switzerland. To address these questions in detail, a de novo cost-minimisation and a budget impact model have been developed. The results from our meta-analyses showed no differences for the important and critical outcomes between infliximab reference product and

biosimilar, which suggests that a cost-minimisation analysis (CMA) is the appropriate economic evaluation strategy. CMA is generally considered to be appropriate to inform biosimilar reimbursement if a reference product is available as standard of care.[173–175]

8.3.2 Perspective

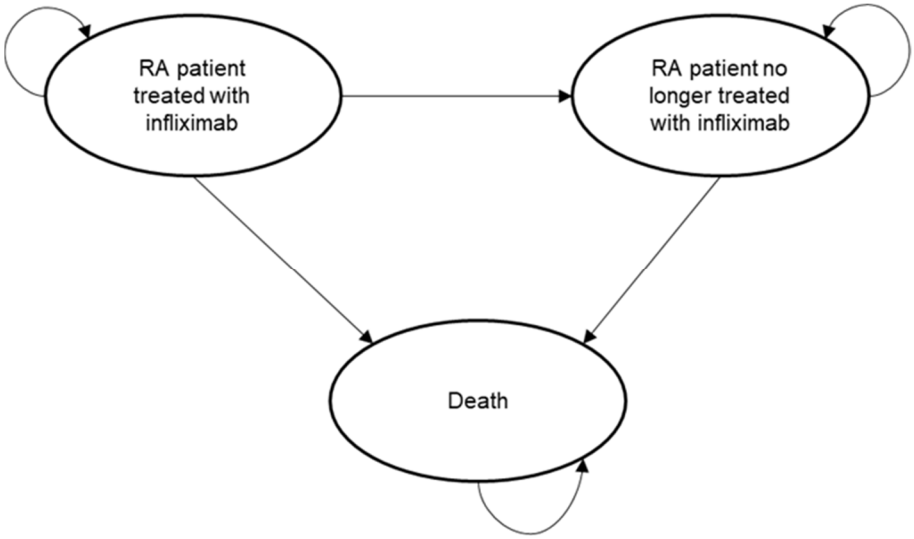
Both, the CMA and the BIA, were built from a health care payer perspective. Costs of health care services covered by the Swiss mandatory health insurance were analysed, irrespective of the actual payer (mandatory health insurance, other social insurance, government, out-of-pocket). The analysis did not include indirect costs due to productivity losses and additional non-medical costs for patients, such as travel costs.

8.3.3 Cost-minimisation analysis

8.3.3.1 Structure of the model

The CMA focused on costs. Provided that the treatments under investigation have similar outcomes (including the risk for adverse events), the only cost aspect that differs between infliximab reference product and infliximab biosimilar is drug costs. For PICO 2, we also considered additional administration and monitoring costs related to the switch from infliximab reference product to infliximab biosimilar. A Markov model that considers treatment discontinuation and mortality was used for this CMA (***Figure 15***). The cycle length of the model was 6 months which is in line with previous models.[176] A half-cycle correction was implemented to account that transitions can occur at any point during the cycle.

Figure 15 Structure of the Markov model



Populations differed between PICOs:

- PICO 1: Patients with RA not responding to DMARDs
- PICO 2: Patients with RA not responding to DMARDs and currently on infliximab reference product

Treatment strategies modelled also differed between PICOs:

- PICO 1:
    - Intervention: Initiate treatment with infliximab reference product
    - Comparator: Initiate treatment with infliximab biosimilar
- PICO 2:
    - Intervention: Continue treatment with infliximab reference product
    - Comparator: Switch to treatment with infliximab biosimilar

8.3.3.2 Time horizon

The model used a lifetime time horizon for the base case analysis. This was implemented in such a way that the population could reach a maximum age of 100 years. As the starting age of the cohort was 54 years (details see ***Section 8.3.3.4***), this corresponds to a time horizon of 46 years. Alternative time horizons of 5, 10 and 20 years were investigated as part of the scenario analysis.

8.3.3.3 Discounting

Future costs were discounted at 3% per annum in the base case analysis. Alternative discount rates of 1% and 5% were investigated as part of the sensitivity analysis.

8.3.3.4 Population

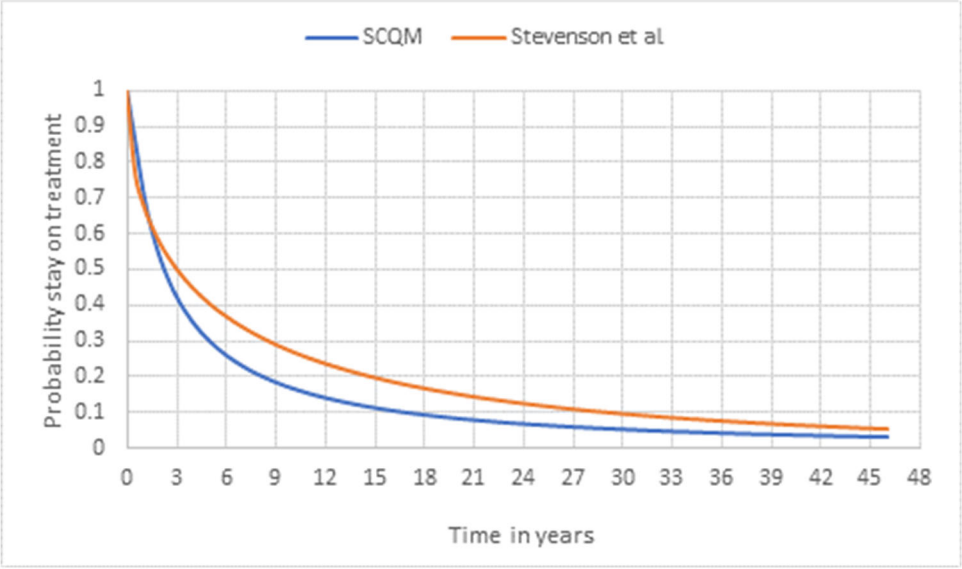
We modelled an RA infliximab population based on information from the Swiss Clinical Quality Management Registry (SCQM).[177] This allowed us to use real-world data from daily clinical practice in Switzerland. Details about SCQM are described elsewhere.[178] The starting age of the modelled cohort was 54.11 years, which corresponds to the mean age at treatment initiation of all infliximab RA patients documented in SCQM.[177] Furthermore, our cohort consists of 74.4% female and 25.6% male patients and mean body weight was 65.48 kg for females and 80.51 for males.[177]

8.3.3.5 Treatment discontinuation

In the base case analysis, we modelled treatment discontinuation based on data from RA infliximab patients from SCQM. For a scenario analysis, we used information from an RCT investigating the infliximab reference product in RA patients to model treatment discontinuation.

We modelled treatment discontinuation based on a Kaplan-Meier analysis of drug retention in all infliximab RA patients documented in the SCQM in the base case analysis (***Appendix 13.8***).[177] We used the same approach described by the Innovation and Value Initiative's individual patient simulation model for rheumatoid arthritis (IVI-RA model)[179] to reconstruct the individual patient level data from the SCQM Kaplan-Meier curve without introducing substantial bias. This model recommends using the algorithm developed by Guyot *et al.*[180], which has demonstrated to have a high degree of accuracy. Consistent with the IVI-RA model, which modelled treatment discontinuation using US RA patient registry data based on Akaike information criterion, the generalized gamma parametric survival model provided good fit to the SCQM data and was used to inform treatment discontinuation transition probabilities in our model. For a scenario analysis, we modelled treatment discontinuation according to an HE model used by Merck Sharp & Dohme for the submission of the infliximab reference product in the UK.[176] This was the only published source to provide the parameters of the identified best-fit (Weibull) function. However, this model was based on data from RCTs and an important limitation of RCTs is that they often lack external validity due to short time horizons and samples that are not representative of the general population. Therefore, treatment discontinuation based on SCQM data was used in the base case analysis. Treatment discontinuation functions used in the base case and scenario analysis are shown in ***Figure 16***.

Figure 16 Treatment discontinuation functions used in the model



Source: Own calculations based on SCQM[177] and Stevenson et al.[176]

Abbreviation: SCQM, Swiss Clinical Quality Management Registry

8.3.3.6 Mortality

Latest Swiss life tables were used to model general mortality.[181,182] In patients with RA, mortality is increased compared to the general population despite the uptake of biologics and methotrexate since the beginning of the 21st century.[67,183–186] However, whereas patients receiving TNF inhibitors have a more active disease and are more likely to get injection-site infections, they experience a lower mortality rate compared to those treated with methotrexate only.[187,188] It is reasonable to extrapolate this evidence to patients treated with infliximab because mortality does not differ across patients treated with different TNF inhibitors.[189] As there is no clear evidence about an increased risk of mortality in RA patients using infliximab or other TNF inhibitors, we assume that mortality of our modelled population does not differ from the general Swiss population.

8.3.3.7 Resource use

We assume that infliximab treatment is initiated with the dose recommended in the product leaflet (i.e. 3 mg/kg at week 0, 2, 6 and every 8 weeks thereafter) and this dose is maintained during the first cycle of our model (first six months). From the second cycle on, we use 3.75 mg/kg, which corresponds to the mean dosage reported for RA patient with infliximab in SCQM.[177]

For PICO 2, we use 3.75 mg/kg during all cycles. Based on input from clinical experts and in line with Gibofsky *et al.*[163], we assume that 30 minutes of additional physician time is needed for switching patients from the reference product to biosimilars. Furthermore, we assume that additional lab test are required for monitoring reasons when switching patients.[163] According to clinical experts, lab tests include: alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, C-reactive protein, gamma-glutamyltransferase, hemogram, creatinine and blood sedimentation reaction. We further assume that these lab tests have to be done twice due to the switch.

8.3.3.8 Cost per unit

Drug costs for infliximab reference product and biosimilars were estimated based on official drug prices available from the latest (January 2021) specialties list issued by the Federal Office of Public Health.[190] Based on input from clinical experts, we assume that vial sharing is not in place.

For the additional physician time required for the switch, rates according to the Swiss medical tarif code for outpatient services (Tarmed) were applied (position 0.1580 (Behandlung durch den Facharzt für

Rheumatologie, pro 5 Min.); details ***see Appendix 13.8***).[191] The costs of the consultations were calculated by multiplying the resulting tax points according to Tarmed with the average of the tax point values set by the cantons.[192]

Unit costs for the lab tests were taken from the Analysenliste issued by the FOPH (positions: 1020.00 (alanine aminotransferase), 1027.00 (alkaline phosphatase), 1093.00 (aspartate aminotransferase), 1245.00 (C-reactive protein), 1341.00 (gamma-glutamyltransferase), 1371.00 (hemogram II), 1509.00 (creatinine) and 1666.00 (blood sedimentation reaction); details ***see Appendix 13.8***).[193]
Costs for blood sampling were based on Tarmed (details ***see Appendix 13.8***).[191]

8.3.3.9 Sensitivity analysis

We conducted several univariate sensitivity analyses and scenario analyses:

- Univariate sensitivity analyses:
    - Discounting: 1% and 5% per annum
    - Body weight: lower and upper bound of 95% confidence interval from SCQM
- Scenario analyses:
    - Time horizon: 5, 10 and 20 years
    - Treatment discontinuation: Based on Stevenson et al. (HE model used by Merck Sharp & Dohme for the submission of the infliximab reference product in the UK; used data from RCT)
    - Additional administration and monitoring costs (only for PICO 2): Lower bound: No additional switch costs (no extra physician time and lab tests); upper bound: Twice the resource use from the base case (i.e. 60 minutes physician time and four times the whole set of lab tests)

8.3.3.10 Overview of CMA model input parameters and data sources

Table 25 provides an overview of the model input parameters and data sources.

Table 25 Overview of CMA model input parameters and data sources

Parameter	Description	Main	Scenario	Source	Source for sensitivity
Cohort characteristics					
Age	Average age of hypothetical cohort at model entry (years)	54.1 (95%CI 53.2-55.0)	No	SCQM[177]	-
Women (%)	Percentage of cohort being female	74.4%	No	SCQM[177]	SCQM[177]
Female weight	Mean bodyweight in females (in kg)	65.5 (95%CI 64.3-66.7)	64.3, 66.7	SCQM[177]	SCQM[177]
Male weight	Mean bodyweight in males (in kg)	80.5 (95%CI 78.3-82.7)	78.3, 82.7	SCQM[177]	SCQM[177]
Resource use					
Initiation dose	Infliximab dose in mg per kg body weight in the initiation period	3.0	No	Product leaflet	-
Dose	Infliximab dose in mg per kg body weight	3.75 (95%CI 3.7-3.8)	3.7, 3.8	SCQM[177]	SCQM[177]
Physician time	Additional physician time due to switch (min, per switch)	30	60	Gibofsky *et al.*[163] and clinical experts	Glintborg *et al.*[194]
Lab tests	Additional sets of lab tests due to switch (per switch)	2	4	Clinical experts	Glintborg *et al.*[194]
Unit cost					
Infliximab reference product cost	Costs reference product (Remicade®)	CHF 830.90 for 100 mg	No	Spezialitätenliste[190]	-
Infliximab biosimilars cost	Costs biosimilar (Remsima®, Inflectra®)	CHF 627.25 for 100 mg	No	Spezialitätenliste[190]	-
Physician cost	Costs per unit of additional physician time due to switch (per 5 min)	CHF 17.21	No	TARMED[191]	-
Lab cost	Costs for set of lab test (8 additional lab tests) due to switch	CHF 39.63	No	Analysenliste[193]	-

Note: Numbers are rounded for presentation purposes

8.3.4 Budget impact analysis

Based on the results from the CMA, the budget impact was estimated.

8.3.4.1 Time horizon

The time horizon for the BIA was five years, which is in line with BIAs identified in the scoping report.

8.3.4.2 Target population

The target population for the BIA was estimated based on the size of the Swiss adult population aged 18 to 75 years old as reported by the Federal Statistical Office for the end of 2019.[195] The age restriction (18 to 75 years old) is based on the inclusion criteria in the RCTs investigated in the meta-analyses conducted as part of this HTA report. Future population changes were assumed to be similar to the change from 2018 to 2019.

Target population for PICO 1

The population relevant for PICO 1 are the annual incident RA patients eligible for infliximab. Incidence of RA for Switzerland was assumed to be 24.38 (95% CI 21.9 to 27.42) per 100'000 persons based on the Global Burden of Disease (GBD) study.[196] To estimate the RA patients eligible for infliximab, we used three different scenarios:

- Base case scenario: For the base case analysis, we used data from SCQM.[177] In the six quarters from Q2 2019 to Q3 2020 on average 3.6% of RA patients were treated with infliximab.
- Lower bound scenario: RA patients eligible for bDMARD therapy was based on the research by Aladul *et al*.[159], where 10% of RA patients were eligible for bDMARDs. Market share of infliximab (reference product and biosimilars) in RA patients treated with bDMARDs was also based on the literature. Kanters *et al*.[165] estimated infliximab market share in RA patients treated with bDMARDs in Germany at approximately 17%. This led to a share of 1.7% of RA patients treated with infliximab.
- Higher bound scenario: We took the difference in percentage points between the base case scenario and the lower bound scenario (3.6% - 1.7%) and added this difference to the base case value (3.6%) to get to the higher bound value of 5.5%.

Target population for PICO 2

The population relevant for PICO 2 are the prevalent RA patients currently treated with infliximab reference product. We assumed a policy intervention for PICO 1 as a prerequisite for a policy intervention for PICO 2. Therefore, only RA patients treated with infliximab reference product in the first year of the

budget impact analysis were considered for the following years. Prevalence of RA for Switzerland was assumed to be 457.82 (95% CI 402.28 to 514.81) per 100'000 persons based on the GBD study.[196] To estimate the share of RA patients treated with infliximab reference product, we used three different scenarios:

- Base case scenario: As for PICO 1, we used data from SCQM to estimate the base case scenario.[177] In the six quarters from Q2 2019 to Q3 2020 on average 3.6% of RA patients were treated with infliximab. Furthermore, data from one of the biggest health insurance companies in Switzerland showed that 77.6% of infliximab patients were treated with the reference product in 2019.[1] Therefore, we assumed that 2.8% of RA patients are treated with infliximab reference product for the base case analysis.
- Lower bound scenario: RA patients eligible for bDMARD therapy was based on the research by Aladul *et al*.[159], where 10% of RA patients were eligible for bDMARDs. Market share of infliximab (reference product and biosimilars) in RA patients treated with bDMARDs was also based on the literature. Kanters *et al*.[165] estimated infliximab market share in RA patients treated with bDMARDs in Germany at approximately 17%. This led to a share of 1.7% of RA patients treated with infliximab. Furthermore, we used again the data from one of the biggest health insurance companies in Switzerland who showed that 77.6% of infliximab patients were treated with the reference product in 2019.[1] Therefore, we assumed that 1.3% of RA patients are treated with infliximab reference product for the lower bound analysis.
- Higher bound scenario: We took the difference in percentage points between the base case scenario and the lower bound scenario (2.8% - 1.3%) and added this difference to the base case value (2.8%) to get to the higher bound value of 4.3%.

8.3.4.3 Treatment mix

Treatment mix for PICO 1

Schur *et al.*[1] estimated that 6879 patients were treated with infliximab in Switzerland in 2019. This estimation is based on health insurance claims data from one of the biggest health insurance companies in Switzerland and extrapolated to the whole country considering specifics of their insurees. Furthermore, they estimated that 5335 patients were treated with the infliximab reference product. This corresponds to a share of 77.6%. SCQM also reports shares for the infliximab reference product around 80%.[177] Numbers for previous years are shown in ***Table 26***. The change from 2016 (year when infliximab biosimilars became reimbursed) to 2019 was used to estimate a scenario for the future biosimilar market share without any policy changes (***Table 27***). A reduction to approximately 60% at the level of the whole

country in 5 years seems to be plausible as some cantons in Switzerland report shares of 70% already today.[1]

We assumed two policy scenario changes to estimate a potential budget impact compared to the scenario without any policy changes:

- Base case scenario: The price of the infliximab reference product would be lowered to the one of the biosimilars.
- Alternative scenario: It would be mandatory to initiate treatment with the infliximab biosimilars or deductible for infliximab reference product would be increased or the price of infliximab biosimilars would be further decreased. For such potential policy scenarios we assumed that the use of infliximab reference product would decrease to 10% over 3 years and then stay at this level ***(Table 27***). In addition, we investigated for such potential policy scenarios the impact of a further price decrease of infliximab biosimilars on the budget. Infliximab biosimilars are currently approximately 25% cheaper than the reference product. We increased this difference in the scenario analyses starting with 30% up to a maximum of 70% price decrease.

Table 26 Infliximab reference product and biosimilar use in Switzerland

Year	2015	2016	2017	2018	2019
Number of patients treated with infliximab in total	6'283	6'634	7'124	6'976	6'879
Number of patients treated with infliximab reference product	6'283	6'547	6'626	5'825	5'335
Share of reference product	100.0%	98.7%	93.0%	83.5%	77.6%

Source: Helsana Arzneimittelreports for the corresponding years[1,94,95,197,198]

Table 27 Market share projections for infliximab reference product – PICO 1

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Source
Without policy intervention	77.6%	72.0%	66.9%	62.1%	57.7%	Based on change in recent years (***see Table 26***)
With policy scenario change – alternative scenario	25%	15%	10%	10%	10%	Assumption

Treatment mix for PICO 2

For PICO 2, we assumed that without any policy changes all patients currently treated with infliximab reference product would stay on the reference product.

As for PICO 1, we assumed two policy scenario changes to estimate a potential budget impact compared to the scenario without any policy changes:

- Base case scenario: The price of the infliximab reference product would be lowered to the one of the biosimilars.
- Alternative scenario: Deductible for infliximab reference product would be increased or the price of infliximab biosimilars would be further decreased. For such potential policy scenarios we assumed that the use of infliximab reference product would decrease over the next 5 years to 50%, 40%, 30%, 20% and 10% (scenario 1 with a clear policy change in the first year) or 80%, 60%, 40%, 20% and 0% (scenario 2 with a more distributed policy change over 5 years) (***Table 28***). In addition, we investigated for such potential policy scenarios the impact of a further price decrease of infliximab biosimilars on the budget. Infliximab biosimilars are currently approximately 25% cheaper than the reference product. We increased this difference in the scenario analyses starting with 30% up to a maximum of 70%.

Table 28 Market share projections for infliximab reference product - PICO 2

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Source
Without policy intervention	100%	100%	100%	100%	100%	Based on change in recent years (***see Table 26***)
With policy scenario change – alternative scenario 1	50%	40%	30%	20%	10%	Assumption
With policy scenario change – alternative scenario 2	80%	60%	40%	20%	0%	Assumption

8.3.4.4 Cost per patient

Cost per patient per treatment strategy was based on the results from the CMA (***Table 29***). These costs are based on all the aspects considered in the CMA (**Section 8.3.3**).

Table 29 Drug cost (and switch cost for PICO 2) per patient

Source	Description	Year 1	Year 2	Year 3	Year 4	Year 5
PICO 1						
CMA	CHF/patient on reference treatment	15'342	10'793	8'290	6'711	5'617
CMA	CHF/patient on biosimilar treatment	11'582	8'147	6'258	5'066	4'240
PICO 2						
CMA	CHF/patient on reference treatment	15'052	10'793	8'290	6'711	5'617
CMA	CHF/patient on biosimilar treatment	11'546	8'147	6'258	5'066	4'240

*Note: These numbers are the results from the CMA for the specific years. For PICO 1, these costs are drug costs only. For PICO 2, these costs include drug costs and switch costs (additional physician time and lab tests). Please consider that based on the body weight from SCQM women require 2 vials during the initiation period and 3 vials after initiation and men require 3 vials during initiation and 4 vials afterwards (see **Table 25**). This is the reason why costs do not differ more between PICO 1 and PICO 2.*

8.3.4.5 Scenario analysis

Scenario analysis considered uncertainty regarding target population, treatment mix and price differences between infliximab reference product and biosimilars and are described in chapter 8.3.4.2 and 8.3.4.3.

8.3.4.6 Overview of BIA model input parameters and data sources

Table 30 provides an overview of the model input parameters and data sources.

Table 30 Overview of BIA model input parameters and data sources

Parameter	Description	Main	Source
Population			
Population	Population size in year 1	8'606'033	FSO[195]
Growth	Population growth per year	0.72%	FSO[195]
18-75 group	Proportion of population 18 to 75 years old	74.2%	FSO[195]
Epidemiology			
PICO 1			
RA incidence	Annual incidence rate of RA (cases per 100'000 people)	24.4 (95%CI 21.9-27.4)	GBD study[196]
RA patients eligible for infliximab			
Base case	Percentage of incident cases	3.6%	SCQM[177]
Lower bound	Percentage of incident cases	1.7%	Aladul *et al.*[159]; Kanters et al.[165]
Higher bound	Percentage of incident cases	5.5%	Assumption based on base case and lower bound scenario
PICO 2			
RA prevalence	Prevalence rate of RA (cases per 100'000 people)	457.8 (95%CI 402.3-514.8)	GBD study[196]
RA patients currently treated with infliximab reference product			
Base case	Percentage of prevalent cases	2.8%	SCQM[177]; Schur *et al.*[1]
Lower bound	Percentage of prevalent cases	1.3%	Aladul *et al.*[159]; Kanters et al.[165]; Schur *et al.*[1]
Higher bound	Percentage of prevalent cases	4.3%	Assumption based on base case and lower bound scenario

Note: Numbers are rounded for presentation purposes

8.3.4.7 Technical implementation

The CMA and BIA were implemented in Microsoft Excel.

8.4 Results de novo health economic model

8.4.1 Findings cost-minimisation analysis

8.4.1.1 Base case analysis

Costs of a strategy that involves treatment initiation with the infliximab reference product (intervention), and those of an initiation with its biosimilar (comparator) were calculated for a lifetime time horizon using the parameters described in ***section 8.3***. As the starting age of the cohort was 54 years (details see ***Section 8.3.3.4***), this corresponds to a time horizon of 46 years. As the only difference between the two strategies was assumed to be the unit cost of the medication, costs do not include the total costs of all the resources involved in the treatment of an average RA patient. The estimated costs of initiating treatment with the infliximab reference product amounted to CHF 73'706 per patient in the base case analysis (***Table 31***). The costs of the strategy that involves initiating treatment with the biosimilar was estimated to be CHF 55'641. This renders a difference in drug costs of CHF 18'065 per patient between the two strategies over a lifetime time horizon.

Table 31 Drug costs of infliximab treatment per average RA patient (PICO1)

	Lifetime costs [CHF]
Intervention (treatment initiation with infliximab reference product)	73'706
Comparator (treatment initiation with infliximab biosimilar)	55'641
Difference (base case)	18'065

Note: Starting age of the cohort was 54 years, these drug costs of infliximab treatment per average RA patient correspond to a "lifetime" time horizon of 46 years.

Similar estimates were derived for PICO 2. The estimated costs of continuing treatment with infliximab reference product amounted to CHF 73'417 per patient (***Table 32***). The costs of the strategy that involves switching treatment from the reference product to its biosimilar was estimated to be CHF 55'605 (considering drug costs and costs due to additional physician time and lab tests related to switching from infliximab reference product to biosimilars). This renders a cost difference of CHF 17'812 per patient between the two strategies over a lifetime time horizon.

Table 32 Drug costs and costs due to additional physician time and lab tests related to switching from infliximab reference product to biosimilars per average RA patient (PICO 2)

	Lifetime costs [CHF]
Intervention (continue with infliximab reference product)	73’416
Comparator (switch from infliximab reference product to biosimilar)	55’605
Difference (base case)	17’812

Note: Similar to PICO 1, the starting age of the cohort was 54 years, these drug costs of infliximab treatment per average RA patient correspond to a “lifetime” time horizon of 46 years.

8.4.1.2 Sensitivity analysis

Several univariate sensitivity analyses and scenario analyses were conducted for PICO 1 and PICO 2 (***Table 33 and Table 34***). Time horizon, treatment discontinuation and discount rate had a substantial influence on the results for both PICOs. On the other hand, the uncertainty behind the body weight of the patients and switching costs (only applicable to PICO 2) had a small impact on the results.

For PICO 1, the base case analysis showed that initiating treatment with infliximab reference product costs CHF 18’065 more per patient than using infliximab biosimilars over a lifetime time horizon. The cost difference between the two treatment strategies was lowest when a 5 year time horizon (instead of a lifetime time horizon in the base case analysis) was used (CHF 10’380) and highest when alternative probabilities for treatment discontinuation were used (CHF 23’342).

For PICO 2, the base case analysis showed that staying on the infliximab reference product costs CHF 17’812 more per patient than switching to the infliximab biosimilars. The cost difference between the two treatment strategies was lowest when a 5 year time horizon (instead of a lifetime time horizon in the base case analysis) was used (CHF 10’126) and highest when alternative probabilities for treatment discontinuation were used (CHF 23’088).

Table 33 Univariate sensitivity analysis and scenario analysis (PICO 1)

	Drug costs reference product (intervention) [CHF]	Drug costs biosimilar (comparator) [CHF]	Drug cost difference (intervention – comparator) [CHF]	Cost difference to base case scenario [%]
Base case	**73'706**	**55'641**	**18'065**	-
Discounting 1%	87'366	65'953	21'413	+19%
Discounting 5%	64'367	48'591	15'776	-13%
Body weight lower bound	69'026	52'108	16'918	-6%
Body weight upper bound	75'252	56'808	18'444	+2%
Time horizon 5 years	42'349	31'970	10'380	-43%
Time horizon 10 years	57'350	43'294	14'056	-22%
Time horizon 20 years	68'804	51'940	16'864	-7%
Treatment discontinuation alternative scenario	95'235	71'894	23'342	+29%

Table 34 Univariate sensitivity analysis and scenario analysis (PICO 2)

	Costs reference product (intervention) [CHF]	Costs biosimilar (comparator) [CHF]	Cost difference (intervention – comparator) [CHF]	Cost difference to base case scenario [%]
Base case	**73'416**	**55'605**	**17'812**	**-**
Discounting 1%	87'076	65'917	21'159	+19%
Discounting 5%	64'077	48'554	15'522	-13%
Body weight lower bound	68'390	51'811	16'580	-7%
Body weight upper bound	73'416	55'605	17'812	0%
Time horizon 5 years	42'059	31'933	10'126	-43%
Time horizon 10 years	57'060	43'257	13'803	-23%
Time horizon 20 years	68'514	51'904	16'610	-7%
Treatment discontinuation alternative scenario	94'946	71'857	23'088	+31%
No additional switch costs (physician time and lab tests)	73'416	55'422	17'994	+1%
Twice the switch costs from the base case scenario (60 minutes physician time and four times the whole set of lab tests)	73'416	55'787	17'629	-1%

8.4.2 Findings budget impact analysis

8.4.2.1 Base case analysis

The budget impact analysis showed for PICO 1 savings of CHF 1.58 million (Mio.) over a time horizon of 5 years for approximately 60 annual incident RA patients eligible for treatment initiation with infliximab biosimilar (***Table 35***). For PICO 2, savings amounted to CHF 9.32 million based on approximately 1'000 prevalent RA patients currently treated with the infliximab reference product (***Table 36***).

Table 35 Results budget impact analysis (PICO 1)

	Year 1	Year 2	Year 3	Year 4	Year 5
Population 18-75 age	6'361'737	6'407'531	6'453'654	6'500'109	6'546'899
Incident RA cases	1'551	1'562	1'573	1'585	1'596
New infliximab eligible patients	56	56	57	57	57
Costs with no policy change [Mio. CHF]	0.81	1.37	1.80	2.14	2.43
Costs with potential policy change (i.e. decrease price of reference product) [Mio. CHF]	0.65	1.11	1.46	1.76	2.01
Annual budget impact [Mio. CHF]	-0.16	-0.27	-0.34	-0.39	-0.42
5-year budget impact [Mio. CHF]	- 1.58				

Table 36 Results budget impact analysis (PICO 2)

	Year 1	Year 2	Year 3	Year 4	Year 5
Population 18-75 age	6'361'737	Not relevant*	Not relevant*	Not relevant*	Not relevant*
Prevalent RA cases	29'125	Not relevant*	Not relevant*	Not relevant*	Not relevant*
RA patients currently treated with infliximab	1'049	747	555	441	364
Costs with no policy change [Mio. CHF]	12.48	8.78	6.75	5.46	4.57
Costs with potential policy change (i.e. decrease price of reference product) [Mio. CHF]	9.42	6.63	5.09	4.12	3.45
Annual budget impact [Mio. CHF]	-3.06	-2.15	-1.65	-1.34	-1.12
5-year budget impact [Mio. CHF]	-9.32				

8.4.2.2 Sensitivity analysis

When considering the uncertainty behind the eligible patient population and the future treatment mix, cost savings for PICO 1 ranged from CHF 0.58 million (alternative policy scenario and assuming that 1.7% (instead of 3.6% in the base case scenario) of incident RA cases would be eligible for infliximab) to 4.78 million (alternative policy scenario assuming that the price of infliximab biosimilars would be lowered to 70% of the current price of the reference product) (base case: CHF 1.58 million). For PICO 2, this range was from CHF 2.20 million (alternative policy scenario and assuming that 1.3% (instead of 2.8% in the base case scenario) of prevalent RA cases are currently treated with infliximab) to CHF 17.30 million (alternative policy scenario assuming that the price of infliximab biosimilars would be lowered to 70% of the current price of the reference product) (base case: CHF 9.32 million). Results of the sensitivity analysis are shown in ***Table 37*** and ***Table 38*** and ***Figure 17*** to ***Figure 19***.

Table 37 Results sensitivity analysis budget impact (PICO 1)

	Year 1	Year 2	Year 3	Year 4	Year 5	Sum over 5 years
With policy scenario change – base case scenario						
Population base case scenario (based on data from SCQM) [Mio. CHF]	-0.16	-0.27	-0.34	-0.39	-0.42	-1.58
Population lower bound scenario (based on international literature) [Mio. CHF]	-0.08	-0.13	-0.16	-0.18	-0.20	-0.74
Population upper bound scenario (based on lower bound and base case) [Mio. CHF]	-0.25	-0.41	-0.52	-0.59	-0.64	-2.41
With policy scenario change – alternative scenario						
Population base case scenario (based on data from SCQM) [Mio. CHF]	-0.11	-0.20	-0.27	-0.31	-0.34	-1.23
Population lower bound scenario (based on international literature) [Mio. CHF]	-0.05	-0.09	-0.13	-0.15	-0.16	-0.58
Population upper bound scenario (based on lower bound and base case) [Mio. CHF]	-0.17	-0.30	-0.41	-0.47	-0.52	-1.87
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 30% [Mio. CHF]	-0.15	-0.26	-0.36	-0.42	-0.47	-1.65
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 40% [Mio. CHF]	-0.21	-0.38	-0.52	-0.62	-0.70	-2.44
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 50% [Mio. CHF]	-0.27	-0.50	-0.69	-0.82	-0.93	-3.22

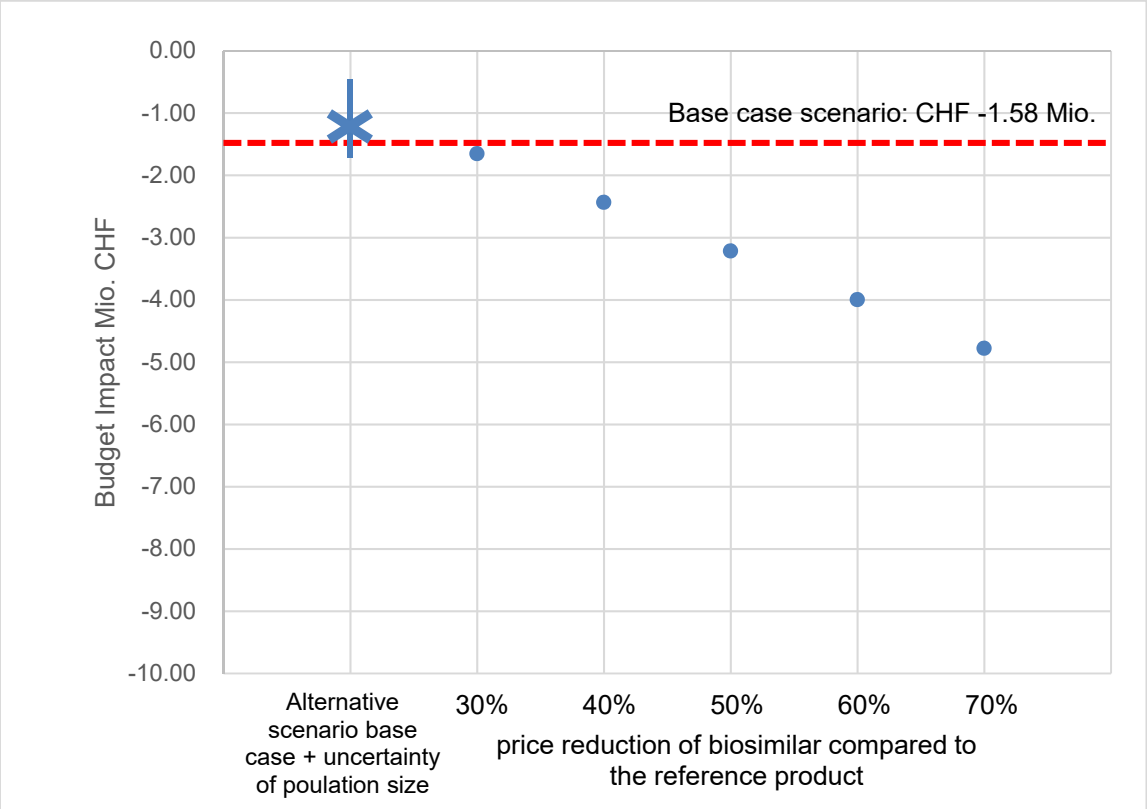
	Year 1	Year 2	Year 3	Year 4	Year 5	Sum over 5 years
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 60% [Mio. CHF]	-0.34	-0.62	-0.85	-1.03	-1.17	-4.00
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 70% [Mio. CHF]	-0.40	-0.74	-1.01	-1.23	-1.40	-4.78

Table 38 Results sensitivity analysis budget impact (PICO 2)

	Year 1	Year 2	Year 3	Year 4	Year 5	Sum over 5 years
With policy scenario change – base case scenario						
Population base case scenario (based on data from SCQM) [Mio. CHF]	-3.06	-2.15	-1.65	-1.34	-1.12	-9.32
Population lower bound scenario (based on international literature) [Mio. CHF]	-1.44	-1.02	-0.78	-0.63	-0.53	-4.40
Population upper bound scenario (based on lower bound and base case) [Mio. CHF]	-4.67	-3.29	-2.53	-2.04	-1.71	-14.24
With policy scenario change – alternative scenario 1						
Population base case scenario (based on data from SCQM) [Mio. CHF]	-1.53	-1.29	-1.16	-1.07	-1.01	-6.06
Population lower bound scenario (based on international literature) [Mio. CHF]	-0.72	-0.61	-0.55	-0.51	-0.48	-2.86
Population upper bound scenario (based on lower bound and base case) [Mio. CHF]	-2.34	-1.97	-1.77	-1.64	-1.54	-9.25
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 30% [Mio. CHF]	-1.87	-1.58	-1.42	-1.31	-1.23	-7.41
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 40% [Mio. CHF]	-2.50	-2.11	-1.89	-1.75	-1.65	-9.89
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 50% [Mio. CHF]	-3.12	-2.63	-2.36	-2.18	-2.06	-12.36
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 60% [Mio. CHF]	-3.74	-3.16	-2.83	-2.62	-2.47	-14.83

	Year 1	Year 2	Year 3	Year 4	Year 5	Sum over 5 years
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 70% [Mio. CHF]	-4.37	-3.69	-3.31	-3.06	-2.88	-17.30
With policy scenario change – alternative scenario 2						
Population base case scenario (based on data from SCQM) [Mio. CHF]	-0.61	-0.86	-0.99	-1.07	-1.12	-4.66
Population lower bound scenario (based on international literature) [Mio. CHF]	-0.29	-0.41	-0.47	-0.51	-0.53	-2.20
Population upper bound scenario (based on lower bound and base case) [Mio. CHF]	-0.93	-1.32	-1.52	-1.64	-1.71	-7.11
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 30% [Mio. CHF]	-0.75	-1.05	-1.21	-1.31	-1.37	-5.70
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 40% [Mio. CHF]	-1.00	-1.41	-1.62	-1.75	-1.83	-7.60
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 50% [Mio. CHF]	-1.25	-1.76	-2.02	-2.18	-2.29	-9.50
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 60% [Mio. CHF]	-1.50	-2.11	-2.43	-2.62	-2.74	-11.40
Population base case scenario (based on data from SCQM) and price difference between reference product and biosimilars at 70% [Mio. CHF]	-1.75	-2.46	-2.83	-3.06	-3.20	-13.30

Figure 17 Sensitivity analysis budget impact (PICO 1)

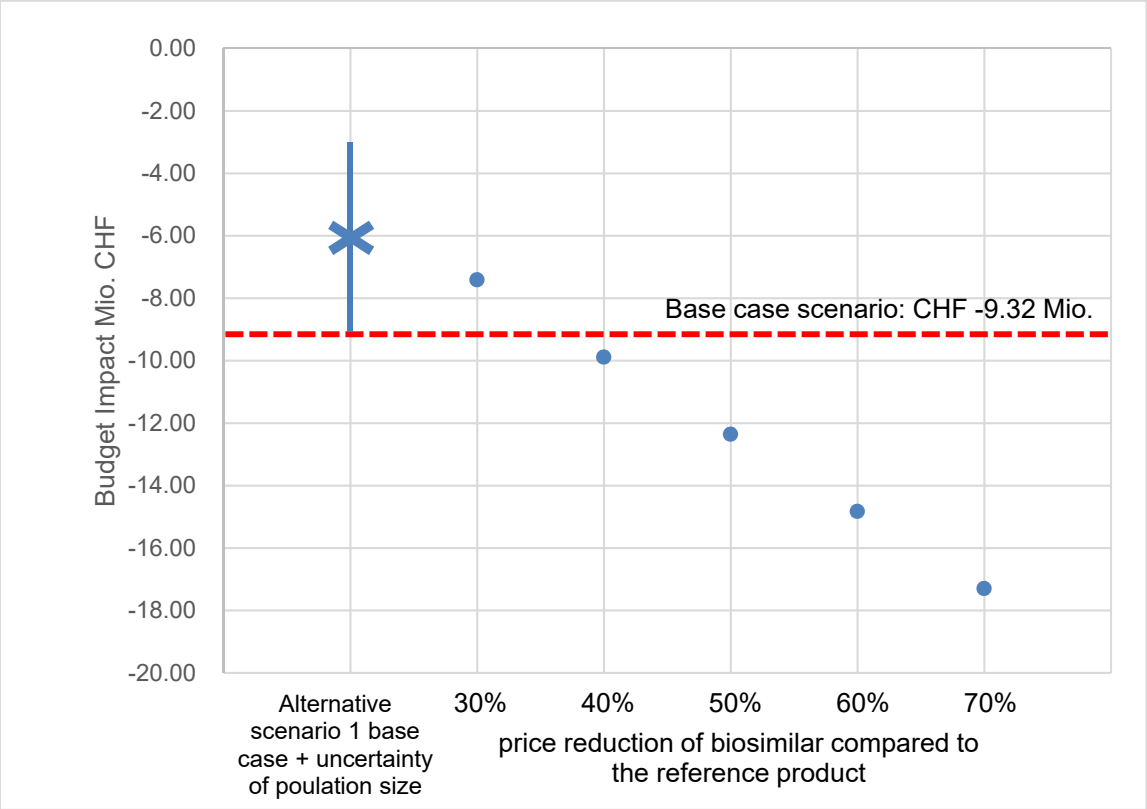


Base case scenario: Population: data from SCQM, Treatment mix: The price of the infliximab reference product would be lowered to the one of the biosimilars (i.e. same prices for biosimilars and reference product, market shares do not matter).

Alternative scenario base case: Population: data from SCQM, Drug costs: The current price difference between infliximab biosimilar and infliximab reference product remains (25%), Market share: Due to policy intervention, the market share of infliximab reference product would decrease over the next 5 years to 25%, 15%, 10%, 10% and 10%.

Sensitivity analysis: upper and lower bound of eligible patients for infliximab are presented (uncertainty of population size), price reduction of biosimilar to promote treatment initiation with biosimilars is modelled.

Figure 18 Sensitivity analysis budget impact (PICO 2, alternative scenario 1)

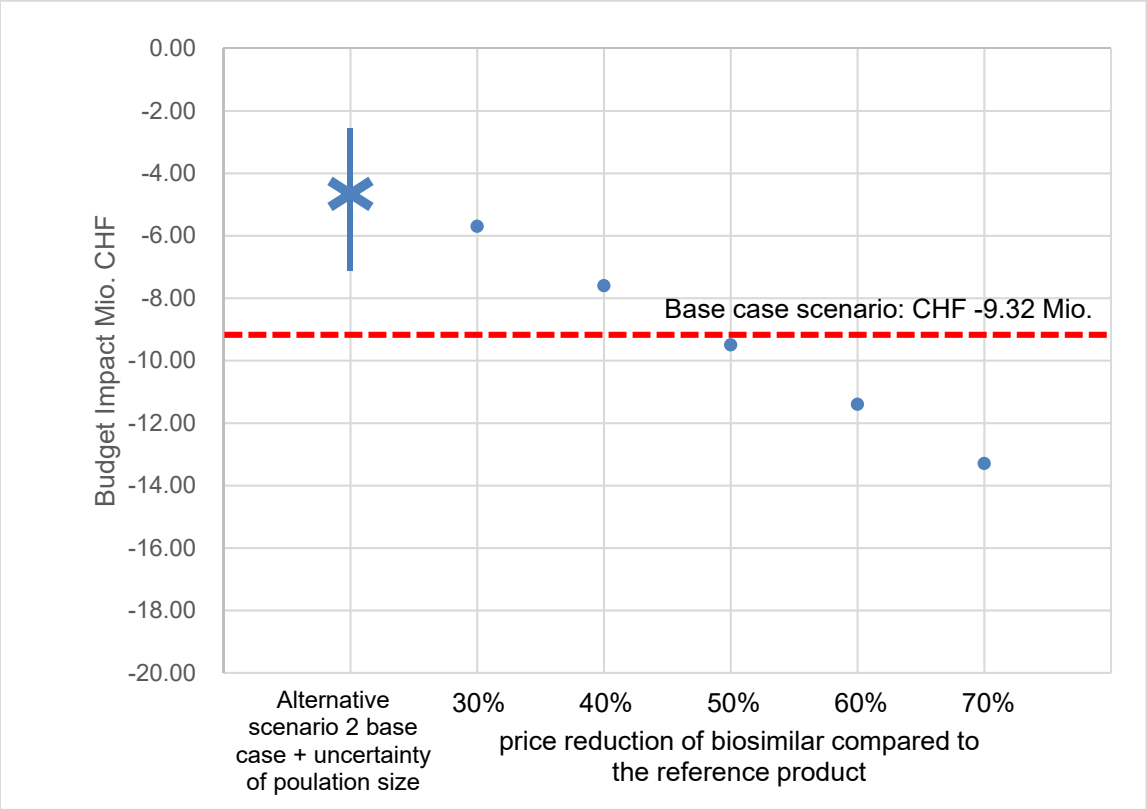


Base case scenario: Population: data from SCQM, Treatment mix: The price of the infliximab reference product would be lowered to the one of the biosimilars (i.e. same prices for biosimilars and reference product, market shares do not matter).

Alternative scenario 1 base case: Population: data from SCQM, Drug costs: The current price difference between infliximab biosimilar and infliximab reference product remains (25%), Market share: Due to policy intervention, the market share of infliximab reference product would decrease over the next 5 years to 50%, 40%, 30%, 20% and 10%.

Sensitivity analysis: upper and lower bound of eligible patients for infliximab are presented (uncertainty of population size), price reduction of biosimilar to promote treatment switch to biosimilars is modelled.

Figure 19 Sensitivity analysis budget impact (PICO 2, alternative scenario 2)



Base case scenario: Population: data from SCQM, Treatment mix: The price of the infliximab reference product would be lowered to the one of the biosimilars (i.e. same prices for biosimilars and reference product, market shares do not matter).

Alternative scenario 2 base case: Population: data from SCQM, Drug costs: The current price difference between infliximab biosimilar and infliximab reference product remains (25%), Market share: Due to policy intervention, the market share of infliximab reference product would decrease over the next 5 years to 80%, 60%, 40%, 20% and 0%.

Sensitivity analysis: upper and lower bound of eligible patients for infliximab are presented (uncertainty of population size), price reduction of biosimilar to promote treatment switch to biosimilars is modelled.

Summary statement cost-minimisation and budget impact

Our de novo health economic model showed that treatment initiation with infliximab reference product costs CHF 18'065 more per patient than using infliximab biosimilars (PICO 1) considering a lifetime time horizon. This cost difference is solely based on differences in drug costs. The sensitivity analysis showed that this difference in drug cost ranged between CHF 10'380 (for a scenario in which a time horizon of 5 years was used instead of a lifetime time horizon in the base case analysis) to CHF 23'342 (for a scenario using alternative probabilities for treatment discontinuation over a lifetime time horizon).

Staying on the infliximab reference product costs CHF 17'812 more per patient than switching to the infliximab biosimilars over a lifetime time horizon (PICO 2). This cost difference considers drug cost as well as additional physician time and lab tests that may be required related to the switch. The cost difference estimated in the sensitivity analysis ranged between CHF 10'126 (for a scenario in which a time horizon of 5 years was used instead of a lifetime time horizon in the base case analysis) and CHF 23'088 (for a scenario using alternative probabilities for treatment discontinuation over a lifetime time horizon).

The budget impact analysis assumed policy scenarios in which the price of the infliximab reference product would be decreased or the use of biosimilars promoted. Cost savings were estimated at CHF 1.58 million over 5 years for approximately 60 annual incident RA patients eligible for treatment initiation with infliximab biosimilar and assuming that the price of the infliximab reference product would be lowered to the one of biosimilars. When considering the uncertainty behind the eligible patient population and the policy intervention, cost savings ranged from CHF 0.58 million for a lower bound population scenario to 4.78 million for an extreme scenario assuming that the price of the infliximab biosimilar would be lowered to 70% of the current price of the reference product.

For PICO 2, savings amounted to CHF 9.32 million in the base case analysis over 5 years based on approximately 1'000 prevalent RA patients currently treated with the infliximab reference product and assuming that the price of the infliximab reference product would be lowered to the one of biosimilars. The budget impact ranged from CHF 2.20 million (for a lower bound population scenario) to CHF 17.30 million (for an extreme scenario assuming that the price of the infliximab biosimilar would be lowered to 70% of the current price of the reference product).

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9 Ethical, legal, social and organisational issues

To address the ELSO issues, we first reviewed the literature. In a second step, we formulated and discussed a range of questions further investigating ethical and legal issues based on the HTA Core Model®[108]. For ethical issues, we also used the "Hofmann catalogue".[111,112] For legal issues, we also took into consideration a checklist designed for the Swiss legal system.[110]

9.1 Methodology ethical, legal, social and organisational issues

9.1.1 Databases and search strategy

9.1.1.1 Search strategies and data sources

We developed search strategies for ELSO outcomes in collaboration with a medical librarian (***see Appendix 13.9***). 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 13.9***). 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 13.3***).

9.1.1.2 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 39***). However, we imposed no study design restrictions as we expected discussions of ELSO outcomes to be presented in a variety of study designs.

Table 39 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.

9.1.1.3 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.[121]

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.

9.1.2 Assessment of quality of evidence

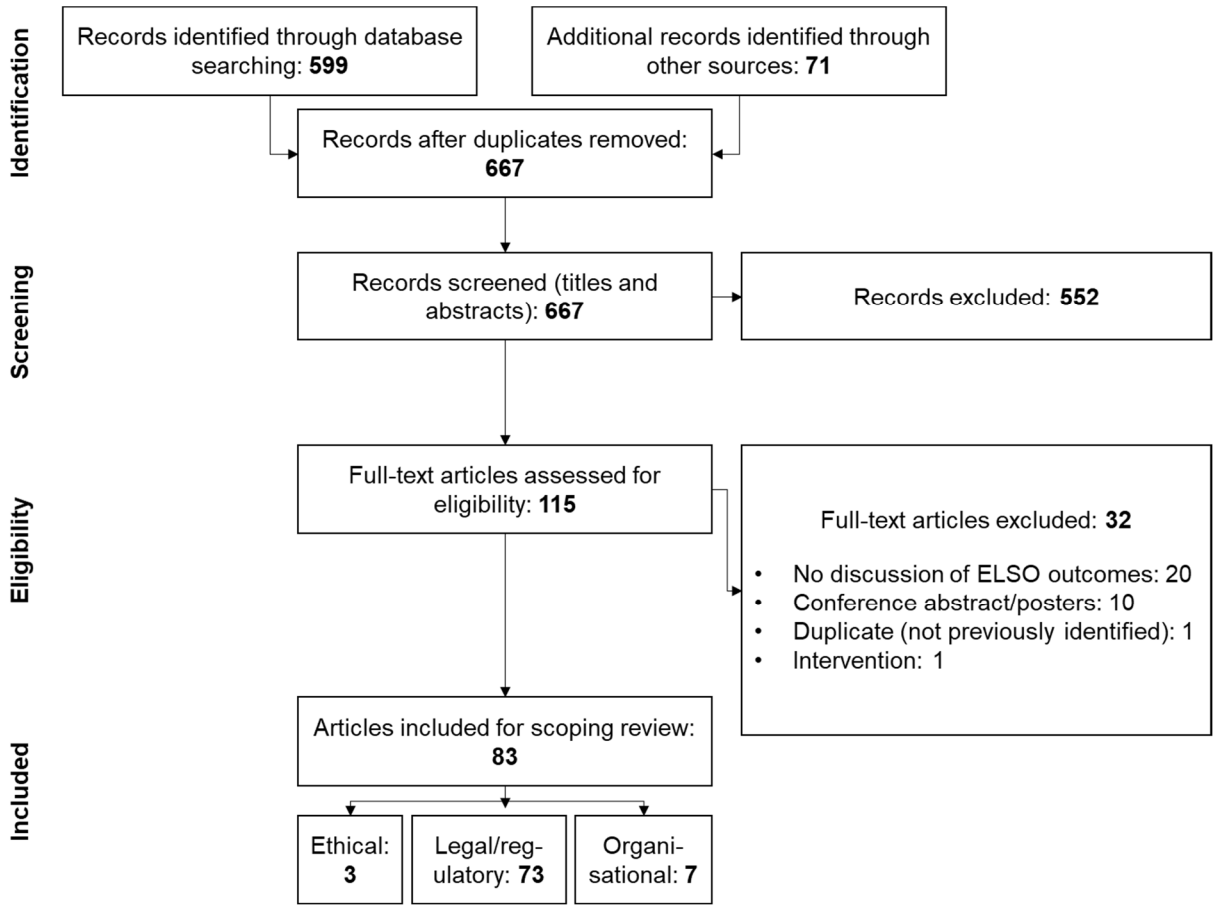
The quality of evidence for ELSO outcomes was not formally assessed.

9.2 Results ethical, legal, social and organisational issues

9.2.1 PRISMA flow diagram

The search for evidence on ELSO outcomes yielded 599 hits from literature databases and 71 hits from other sources (***Figure 20***).

Figure 20 PRISMA flow diagram for ELSO issues search



Abbreviation: ELSO, Ethical, Legal, Social, Organisational; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[133]

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 13.10***). Eighty-three articles were retained for the HTA, including 73 studies discussing, reviewing, or reflecting on legal/regulatory issues, 7 discussing organizational issues, and 3 discussing ethical issues. We identified no studies on social issues associated with biosimilars.

9.2.2 Evidence table

Characteristics of the studies reporting on ELSO outcomes are shown in ***Appendix table 9***.

CoI and funding: Not all studies reported on CoI and study funding. Several studies were publications by state agencies where CoI and study funding were 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 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* an exhaustive review of the literature. Instead, we used these searches to identify important sources for target countries and retrieve sufficient information on ELSO 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.

9.2.3 Findings 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[199], we identified two studies discussing ethical implications of non-medical induced switching from reference products to biosimilars.[200,201] Both studies used as their premise the uncertainty around the safety of non-medical induced 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[201] to a "robust and thorough disclosure of relevant risks, benefits and reasonable alternatives"[200].

In addition to these literature findings, we formulate a range of questions and discuss them briefly in the face of the current evidence given in this 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"[108]. 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[202], we will use the axiological approach in this HTA report. 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"[111,112] 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.[203–205] 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"[112]. Yet, we will address selected questions from the catalogue 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[112].

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

On the basis of current evidence as laid out in this HTA we assume that there is equivalent effectiveness, safety and quality for the infliximab reference product and biosimilars in patients with RA.[104] 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.[81,82,206] Biosimilars may deviate from the reference product only as much as different lots would deviate from each other.[80] In summary, treatment initiation with biosimilars *per se* are not deemed to pose a problem endangering or harming patients.

For PICO 2 (stay on infliximab reference product vs non-medical switch from infliximab reference product to infliximab biosimilar) there is evidence for equivalent effectiveness and safety. However, the certainty of evidence was rated as moderate or low for the relevant outcomes. 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 9.2.4***.

Q12: Are there any related technologies that have turned out to 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 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"[112]. 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).[84] In the face of justice as one of the moral principles in biomedical ethics, according to Beauchamp and Childress, benefits and risks as well as costs need to be taken into account.[207] Reducing costs for biosimilars and subsequently for reference product will allow to spend resources in other areas.

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.

Therapeutic autonomy in general

Therapeutic autonomy or therapeutic freedom in general can be defined as a right of health professions to protect their patients and themselves from criteria and guidance not based on the current scientific evidence or non-medical reasons. Therapeutic autonomy could be claimed in a case, for instance, where a government would simply overrule guidelines to reduce therapeutic standards neglecting the evidence. Thus, therapeutic autonomy can be understood analogous to the right of freedom of research, a right that likewise protects researchers from being forced to examine certain topics and to apply methods that are not scientifically sound.

However, if the choice between a reference product and its biosimilars, in our case the switch from infliximab reference product to its biosimilars in patients with RA, is a sound and equivalent alternative based solely on adequate scientific evidence the right to therapeutic autonomy is not touched.[207] To the contrary, we would argue, as Beauchamp and Childress explain in their groundbreaking ethical work,

given the evidence of this HTA, two principles could guide the decision grounded in therapeutic autonomy: beneficence and non-maleficence. These ethical principles point towards decisions based on evidence that implies equivalence in safety, quality and effectiveness. Furthermore, therapeutic autonomy and fair distribution of services must also be balanced (principle of justice, see above). Fair distribution of health services in the Swiss health care system is warranted according to Art. 56 Krankenversicherungsgesetz [KVG] where it says that medical services should be delivered in an effective, appropriate and efficient manner in order to protect the health care insurance system based on solidarity from improper utilization. In the context of KVG and the ethical principle of fair distribution based on efficient delivery of care, therapeutic autonomy should not be purported as the choice amongst a number of equivalent therapeutic regimen with the same efficacy, quality and safety according to systematic evidence irrespective of other relevant factors such as price and (health) economic considerations.

Therapeutic autonomy on the basis of the evidence

As the evidence 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.

Furthermore, in order to ensure therapeutic autonomy based on information it seems that health professionals need to be informed about the basic principles of the concept of biosimilars and how they are scientifically assessed as pointed out in an article by Ludwig et al.: “Furthermore, it provides information on scientific principles guiding biosimilar development and regulatory requirements. This should minimise unfounded fears and concerns among clinicians. Additionally, we provide information on the interchangeability between originator products and biosimilars to assist clinicians in making evidence-based, appropriate and cost-effective treatment choices for their patients.”[208]

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 the effectiveness, the quality and the safety of biosimilars are non-inferior to infliximab but to, among others, when to switch.

Q16: Can the technology harm the patient?

Switching can harm the patient although evidence (see above) does not point into that direction. 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."[209] 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"[209]. 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.[210]

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 HTA report.

Q33: What are the moral consequences of the HTA Report?

Patients may no longer receive the infliximab reference product, a consequence that according to our overview 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 on ethical issues

The ethical challenges delineated in this report are, from our perspective, the key issues. In conclusion, we do not see severe nor highly controversial ethical issues based on the scientific evidence concerning switching from the reference product to biosimilars of infliximab in patients with RA. In case of changing evidence this should be newly evaluated.

From an ethics perspective, communication and shared decision making in situations of therapeutic switching are crucial. Independent patient information should be provided to caregivers as well as to patients and their families. Physicians should be made aware that switching might have unintended effects on patients in vulnerable situations (e.g., adolescence who have general difficulties to remain adherent, pregnant women who might fear for their baby). As these populations are to be specifically protected, it might be morally advisable to postpone switching to a later period in these patients.

9.2.4 Findings legal issues

Here, we discuss legal aspects and challenges of biosimilars specifically for the Swiss context.

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".[108] 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"[108]

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.[110]

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[211]). Regulation of substitution in Swiss health insurance law (Art. 52a 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[113]; Wildi[212], margin note 76). A revision to this regulation is currently under review in parliament.[213]

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 decided in 2018 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 in 2013 that biosimilars could not be interchanged with the reference product (and with each other) due to concerns about patient safety and immunogenicity.[214] To this day, administrative practice refers to this FOPH statement.[211]

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.[215] A recent report investigating the use of Biosimilars in Switzerland also criticised, that the substitution of biologics is not explicitly permitted in Switzerland.[216]

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[217]) 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[218], 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[212], 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[212] 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 originator product for medical reasons (Art. 38a Paragraph 6 Krankenpflegeleistungsverordnung). This helps to avoid a conflict between therapeutic product and health insurance law. Lack of such a regulation may lead to rather difficult legal questions.[219]

Additional note: It is primarily up to the legislators to decide on the application of the precautionary principle. The SSC recognises a growing need for precautionary measures for modern technologies with a high risk potential. [220] 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. A possible approach might be to design a risk-based regulation: For example, it could be examined if due to a) an (abstract) potential for risk and/or b) scientific evidence, new prescriptions and switch need to be treated differently. It would also have to be examined whether and under what conditions the patients can validly consent to the risk.

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.[221]

Therapeutic freedom does not hold absolutely but is restricted by the legal system (see Giger *et al.*[222], 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.[219,223] 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.[218]

- 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[218] and regarding the appropriate design of traceability and pharmacovigilance ("good pharmacological practice").[224] 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.[216]

Conclusion on legal issues

Interchangeability of biologics in Switzerland is not explicitly regulated by neither the therapeutic products law nor the health insurance law. Furthermore, interchangeability is not part of the regulatory approval of a biosimilar by Swissmedic. The SSC decided in 2018 that biologic reference products and their biosimilars could not just be interchanged ("nicht ohne Weiteres gegeben"). Much more restrictively, the FOPH stated in 2013 that biosimilars could not be interchanged with the reference product (and with each other) due to concerns about patient safety and immunogenicity and to this day, administrative practice refers to this FOPH statement. Consequently, the decision about interchangeability in an individual case rests with treating physicians in compliance with their professional duties and due diligence. Furthermore, there is no definitive legal answer in regard to when interchangeability is admissible from a legal perspective. The more vague the legal requirements for interchangeability, the greater the responsibility of healthcare professionals. This can lead to reluctance regarding the prescription and dispensing of biosimilars. A clarification can be provided by law and/or by professional guidelines.

9.2.5 Findings social issues

We identified no studies on social issues associated with biosimilars. Furthermore, no such issues were encountered throughout the conduct of the HTA.

9.2.6 Findings organisational issues

Organisational issues relate to various policies to (not) promote and (not) implement 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.[115,116,225–230] 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.[114,231]

A recent study by Kobler *et al.*[216] identified different aspects that may influence the use of biosimilars in Switzerland. One issue in Switzerland are the profit margins that depend on the price of a product. As reference products have higher prices compared to biosimilars, they lead to higher profit margins.[232] Therefore, there are financial incentives to use the reference product instead of biosimilars. Furthermore, the price difference between reference products and biosimilars is considered as relatively low. In addition, the storage of biologics is demanding (cold chain, expiry date) and the related financial risk high. Therefore, health care providers prefer to have a limited number of products available and desist from storing infliximab reference product and biosimilar. Several studies also showed that profound patient and physician information and education is crucial for a successful implementation of biosimilars, especially for the therapy switch from the reference product to its biosimilar.[145,146]

Summary statement ethical, legal, social and organisational issues

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There were no severe nor highly controversial ethical issues identified based on the scientific evidence concerning treatment initiation with infliximab reference product versus infliximab biosimilars or switching from the reference product to biosimilars of infliximab in patients with RA. The right to therapeutic autonomy is not touched when treatment initiation with infliximab biosimilar or switching from infliximab reference product to its biosimilars in patients with RA is a sound and equivalent alternative based on adequate scientific evidence.

From a legal perspective, interchangeability of biologics is a key issue. Interchangeability of biologics in Switzerland is not explicitly regulated by neither the therapeutic products law nor the health insurance law. Furthermore, interchangeability is not part of the regulatory approval of a biologic by Swissmedic. The SSC decided in 2018 that biologic reference products and their biosimilars could not just be inter-

changed (“nicht ohne Weiteres gegeben”). Much more restrictively, the FOPH stated in 2013 that biosimilars could not be interchanged with the reference product (and with each other) due to concerns about patient safety and immunogenicity and to this day, administrative practice refers to this FOPH statement. Consequently, the decision about interchangeability in an individual case rests with treating physicians in compliance with their professional duties and due diligence. Furthermore, there is no definitive legal answer in regard to when interchangeability is admissible from a legal perspective. The more vague the legal requirements for interchangeability, the greater the responsibility of healthcare professionals. This can lead to reluctance regarding the prescription and dispensing of biosimilars. A clarification can be provided by law and/or by professional guidelines.

We identified no evidence on social issues associated with the use of biosimilars.

Organisational issues may relate to various policies to (not) promote and to (not) implement biosimilars. Within this context, relevant are the higher profit margins of reference products compared to biosimilars. This leads to a financial incentive to use reference products instead of their biosimilars.

10 Discussion

This HTA report shows evidence that treatment initiation with infliximab biosimilar is as safe and effective as treatment initiation with its reference product. From a health economic point of view, treatment initiation with infliximab reference product compared to treatment initiation with infliximab biosimilars is related to substantial additional drug costs.

Switching from infliximab reference product to its biosimilar compared to continuation of the reference product reveals similar results in safety and efficacy outcomes, whereby this finding is based on only two studies. The health economic analysis showed that treatment continuation with infliximab reference product compared to a switch to infliximab biosimilars is also related to substantial additional drug costs.

Regarding the ELSO domains, we identified two main issues. First, interchangeability of biologics is not explicitly regulated by the Swiss law and increases the responsibility of healthcare professionals. This can lead to reluctance regarding the prescription and dispensing of biosimilars. Second, the higher profit margins of reference products compared to biosimilars may lead to a financial incentive to use reference products instead of their biosimilars.

Efficacy, effectiveness and safety

Our newly conducted meta-analysis is based on nine studies reporting on five RCTs for treatment initiation and on two RCTs for switching to biosimilar and includes most recent studies. The findings regarding efficacy, effectiveness and safety correspond to the ones from previous reviews of RCTs.[124–126,233] One non-systematic review performed a network meta-analysis and found no significant difference between biosimilar- and originator-infliximab in terms of efficacy and safety.[124] Two systematic reviews analysed clinical efficacy and safety via meta-analysis or mixed treatment comparison and concluded that results between infliximab-biosimilar and the reference product were comparable.[125,126] One network meta-analysis investigated the effect on radiographic joint destruction in RA and obtained no difference between original reference product and the biosimilar.[233] However, it still remains a question how efficacy seen in RCTs reflects real-world effectiveness.[234]

Although current evidence does not indicate a difference in outcomes between staying on the infliximab reference product compared to switching to the biosimilar, this finding is based on only two RCTs and the certainty of evidence was rated to be moderate to low. Our findings are in line with several systematic reviews of RWE and RCT studies, which conclude that the available switching data in general do not indicate that switching from a reference product to a biosimilar is associated with major efficacy, safety or immunogenicity issues.[235–238] However, they also point out, that there are evidence gaps and limitations stemming from a lack of a robust design for most of the included studies and that additional data

from sufficiently powered and appropriately statistically analysed clinical trials with long-term follow-ups are needed to explore potential switching risks in various populations and scenarios.[235,237,239,240]

The RCTs investigated patients with definite RA according to the revised 1987 ACR classification criteria, whereas infliximab is now applied earlier in the disease based on the more sensitive ACR/EULAR criteria of 2010. Patients are currently treated according to the 2019 EULAR Recommendations for management of RA with synthetic and biological DMARDs[8] and the 2015 ACR Guideline for the treatment of RA.[50] Consequently, RCTs were conducted in a RA patient population with more advanced disease than today's candidates for treatment with infliximab.

We analysed the RWE studies in relation to treatment discontinuation and nocebo effect. Three studies reported on lower retention rates after switching from the reference product to the biosimilar[140,143,150] and explained the finding by subjective factors such as negative expectations or negative perceptions of the biosimilar known as nocebo effect. This fact points out the importance of patient and physician education and empowerment as demonstrated in one RWE study[140] and highlighted by one systematic review evaluating RWE studies.[239]

Health economic analysis

To the best of our knowledge, the cost-minimisation analysis was the first in the field of RA and infliximab and we were able to parametrize the model with Swiss specific infliximab RA patient data. Model parameters that showed highest impact on the results were the time horizon of the model, the discount rate and treatment discontinuation. In the base case analysis, treatment discontinuation was modelled with data from SCQM. The alternative scenario used lower probabilities of treatment discontinuation which led to a higher difference in drug costs between infliximab reference product and biosimilars. The substantial influence of the discount rate was based on the long-term horizon of the model. Shorter time horizons led to substantially lower cost differences between infliximab reference product and biosimilars, but even with a time horizon of five years cost savings still amounted to CHF 10'000 per RA patient when treatment was initiated by or switched to the biosimilar. Based on the disease and treatment discontinuation data from SCQM, a time horizon of longer than ten years seems to be indicated. However, results differ minimally between a lifetime time horizon and a 20-year time horizon. Potential additional switch costs (physician time and lab tests) for PICO 2 showed a negligible effect on the results. Furthermore, it should be considered that we analysed only drug costs (PICO 1) and drug plus additional switch costs (PICO 2), Total costs of all the resources involved in the treatment of an average RA patient would be substantially higher.[241] In addition, our analysis was performed from a health care payer perspective and included drug costs and additional switch costs covered by the Swiss mandatory health insurance irrespective of the actual payer. However, there is evidence showing that the economic burden for RA patients can be substantial.[242]

Some readers might be surprised by the small difference of the CMA results between PICO 1 and PICO 2. However, this is mainly due to the fact that based on the body weight from SCQM women require 2 vials during the initiation period and 3 vials after initiation and men require 3 vials during initiation and 4 vials afterwards. Nevertheless, two potential issues should be considered for PICO 2. First, treatment discontinuation was modelled similarly to PICO 1. It could be argued that potential nocebo effects would lead to higher probabilities of discontinuation. On the other hand, non-medical switch patients are at a later stage of treatment and probabilities for treatment discontinuation after the switch would be lower compared to initial treatment initiation with infliximab. Lower probabilities of treatment discontinuation would lead to a higher cost difference between infliximab reference product and biosimilars as shown in the scenario analysis. Second, age of patients eligible for PICO 2 might be higher than for PICO 1. Higher age would lead to higher probabilities of death and therefore a smaller cost difference between reference product and biosimilars. Since we had no information on the age of the population for PICO 2, we assumed it would not differ to the one from PICO 1.

The budget impact analysis assumed policy scenarios in which the price of the infliximab reference product would be decreased or the use of biosimilars promoted. Such scenarios led to savings of CHF 1.6 million over a time horizon of 5 years for PICO 1 and CHF 9.3 million for PICO 2. However, there is uncertainty behind the number of RA patients eligible for infliximab (PICO 1) or currently treated with infliximab (PICO 2) as well as potential future policy interventions which all showed a substantial impact on the budget impact. There exist previous studies estimating the potential budget impact of promoting the use of biosimilars in Switzerland. Schur *et al.*[1] estimated potential cost savings related to infliximab at CHF 27 million for 2019 if the price of the infliximab reference product would be lowered to the one of the infliximab biosimilar. Our results seem to be in line with these findings as we only considered infliximab in RA patients. Kobler et al.[216] estimated the potential budget impact of infliximab, etanercept, rituximab, adalimumab, bevacizumab and trastuzumab in all relevant therapeutic areas. They estimated cost savings of CHF 58 million in a scenario where 50% of the treatment initiations would be based on biosimilars and at the same time costs of biosimilars would be decreased to 50% of the costs of the reference products.

Ethical, legal, social and organisational issues

Our examination with the ethical aspect identified no severe nor highly controversial issues based on the scientific evidence concerning treatment initiation with infliximab reference product vs. infliximab biosimilars or switching from the reference product to biosimilars of infliximab in patients with RA. We identified two studies discussing ethical implications of non-medical induced switching from reference products to biosimilars.[200,201] Both studies 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[201] to a “robust and thorough disclosure of relevant risks, benefits and reasonable alternatives”[200]. The ethical review and interpretation in our report concludes that the right to therapeutic autonomy is not touched when treatment initiation with infliximab biosimilar or switching from infliximab reference product to its biosimilars in patients with RA is a sound and equivalent alternative based on adequate scientific evidence.

From a legal perspective, interchangeability of biologics is a key issue, since interchangeability of biologics in Switzerland is not explicitly regulated. The Swiss supreme court and the FOPH stated that biosimilars could not just be interchanged with the reference product (and with each other) due to concerns about patient safety and immunogenicity and to this day, administrative practice refers to this FOPH statement. Consequently, the decision about interchangeability in an individual case rests with treating physicians in compliance with their professional duties and due diligence. The more vague the legal requirements for interchangeability, the greater the responsibility of healthcare professionals. This can lead to reluctance regarding the prescription and dispensing of biosimilars. The introduction of a law specific about interchangeability and substitution regarding biologics and/or professional guidelines could bring clarification.

No studies on social issues associated with biosimilars were identified. Furthermore, no such issues were encountered throughout the conduct of the HTA.

The organisation to promote and implement biosimilars may be hampered by the higher profit margins of reference products compared to biosimilars, which leads to a financial incentive to use reference products instead of their biosimilars. The “Network Biosimilars CH”, which was founded in January 2020 to promote the use of biosimilars in Switzerland and to exploit the potential for savings, refers to this issue as one of their main goals they intend to address, besides education of medical professionals and the broad population and cooperation of stakeholder.[243] Intergenerika has also identified the sales margins as an area for action, along with simplified admission procedure, interchangeability and pricing policy.[244]

Strengths of this HTA

This HTA has several strengths. It systematically reviews the specific research questions posed by the FOPH and evaluates the identified literature in-depth. The newly conducted meta-analysis assesses the evidence including most recent studies. Furthermore, a de novo health economic model was built. This

is the first cost-minimisation analysis in the field of RA and infliximab in Switzerland. The comprehensive and thorough research on Swiss data and the established collaboration with SCQM allowed us to parametrize the cost-minimisation model with Swiss specific RA infliximab population data. The economic evaluation also benefits from the inclusion of data published in the annual drug report of one of the biggest health insurance companies in Switzerland (Helsana). In addition, the ELSO domains were assessed and discussed in detail.

Limitations

Nevertheless, this HTA also has some limitations which we mainly assign to the health economic evaluation. These limitations are primarily related to the uncertainty behind the number of RA patients eligible for infliximab (PICO 1) or currently treated with infliximab (PICO 2) which showed a substantial impact on the budget impact. However, uncertainty was assessed in different sensitivity analyses and all showed cost savings if biosimilars would be promoted. Furthermore, this issue applicable to infliximab for RA is common for drugs used in several indications. In addition, no clear policy guidance (e.g. price reduction of the reference product, reimbursement not exceeding the biosimilar price, price reduction of biosimilar etc.) was available which made it difficult to come up with potential future policy interventions to calculate their potential budget impact. In addition, the use of infliximab has decreased in recent years.[1] This might be especially applicable to RA where new therapies have become available recently (e.g. JAK inhibitors). The higher the market share of such new therapies, the smaller the potential budget impact of infliximab biosimilar compared to its reference product.

Evidence Gap

We identified two areas where more evidence is needed. First, the systematic literature search we performed did not identify any RCTs reporting on switching from biosimilar to the reference product. Second, the evidence for switching from the reference product to biosimilar is only moderate to low. Therefore, RCTs examining switch from infliximab biosimilar to the reference product and more RCTs investigating switch from the reference product to the biosimilar in patients with RA would be beneficial.

11 Conclusions

The review of the existing literature and the conducted meta-analysis of the important outcomes showed comparable clinical efficacy and safety (i) after treatment initiation with infliximab biosimilar compared to its reference product in patients with RA and (ii) after switching from infliximab reference product to biosimilar compared to the continuation of reference product in patients with RA. The certainty of evidence was judged as moderate to high for treatment initiation with infliximab biosimilar compared to the reference product and low to moderate for switching to biosimilar compared to the continuation of reference product. None of the identified studies reported on switching from biosimilar to the reference product.

Our de novo cost-minimisation analysis showed that treatment initiation with infliximab reference product costs CHF 18’065 more per RA patient than using infliximab biosimilars over a lifetime time horizon. This cost difference is solely based on differences in drug costs. When considering uncertainty behind different model parameters, the difference in drug costs ranged between CHF 10’380 and CHF 23’342 per patient. The budget impact analysis assumed policy scenarios in which the price of the infliximab reference product would be decreased or the use of biosimilars promoted. Cost savings were estimated at CHF 1.58 million over a time horizon of 5 years for approximately 60 annual incident RA patients eligible for infliximab with a range between CHF 0.58 million and 4.78 million. Staying on the infliximab reference product costs CHF 17’812 more per patient than switching to the infliximab biosimilars over a lifetime time horizon (range: CHF 10’126 to CHF 23’088). This cost difference considers drug cost as well as additional physician time and lab tests that may be required related to the switch. In the budget impact analysis, savings related to switching to the biosimilar amounted to CHF 9.32 million in the base case scenario over 5 years based on approximately 1’000 prevalent RA patients currently treated with the infliximab reference product. When considering uncertainty behind the eligible patient population (number of RA patients, which are treated with infliximab) and future treatment mix depending on the policy intervention considered, the budget impact ranged from CHF 2.20 million to CHF 17.30 million.

There were no severe nor highly controversial ethical issues identified. From a legal perspective, interchangeability of biologics is a key issue. It is unclear when interchangeability is admissible from a legal perspective. This can lead to reluctance regarding the prescription and dispensing of biosimilars. A clarification can be provided by law and/or by professional guidelines. No evidence on social issues associated with the use of biosimilars were identified. The organisation to promote and implement biosimilars may be hampered by the higher profit margins of reference products compared to biosimilars, which leads to a financial incentive to use reference products instead of their biosimilars.

12 References

1 Schur N, Twerenbold S, Reinau D, *et al.* Helsana-Arzneimittelreport für die Schweiz 2020. Helsana 2020. https://www.helsana.ch/en/helsana-group/about-our-company/health-sciences/drug-report

2 Bundesamt für Gesundheit. Handbuch betreffend die Spezialitätenliste (SL). Bundesamt für Gesundheit 2017. https://www.bag.admin.ch/dam/bag/de/dokumente/kuv-leistungen/bezeichnung-der-leistungen/antragsprozesse-arzneimittel/handbuch-betreffend-die-spezialitaetenliste-gueltig-ab-01.05.2017.pdf.download.pdf/Handbuch%20betreffend%20die%20Spezialit%C3%A4tenliste%20G%C3%BCltig%20ab%2001.05.2017.pdf (accessed 10 Apr 2020).

3 Araújo FC, Fonseca JE, Goncalves J. Switching to biosimilars in inflammatory rheumatic conditions: current knowledge. Eur Med J Rheumatol 2018;5:66–74

4 Yoo DH, Hrycaj P, Miranda P, *et al.* A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013;**72**:1613–20. doi:10.1136/annrheumdis-2012-203090

5 Yoo DH, Racewicz A, Brzezicki J, *et al.* A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. *Arthritis Res Ther* 2016;**18**:82. doi:10.1186/s13075-016-0981-6

6 Yoo DH, Prodanovic N, Jaworski J, *et al.* Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. *Ann Rheum Dis* 2017;**76**:355–63. doi:10.1136/annrheumdis-2015-208786

7 Jørgensen KK, Olsen IC, Goll GL, *et al.* Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* 2017;**389**:2304–16. doi:10.1016/S0140-6736(17)30068-5

8 Smolen JS, Landewé RBM, Bijlsma JWJ, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* Published Online First: 2020. doi:10.1136/annrheumdis-2019-216655

9 Fiehn C, Holle J, Iking-Konert C, *et al.* S2e-Leitlinie: Therapie der rheumatoiden Arthritis mit krankheitsmodifizierenden Medikamenten. *Z Für Rheumatol* 2018;**77**:35–53. doi:10.1007/s00393-018-0481-y

10 SGR. Behandlungsempfehlungen der SGR: TNF-Hemmer. Schweiz. Ges. Für Rheumatol. 2019.https://www.rheuma-net.ch/de/dok/sgr-dokumente/behandlung/therapie/biologics/67-tnf-hemmer/file?force-download=1 (accessed 4 Apr 2020).

11 Smolen JS, van der Heijde D, Machold KP, *et al.* Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2014;**73**:3–5. doi:10.1136/annrheumdis-2013-204317

12 Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet* 2016;**388**:2023–38. doi:10.1016/S0140-6736(16)30173-8

13 Deane KD, Holers VM. The natural history of rheumatoid arthritis. *Clin Ther* 2019;**41**:1256–69. doi:10.1016/j.clinthera.2019.04.028

14 Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. *Lancet* 2010;**376**:1094–108. doi:10.1016/S0140-6736(10)60826-4

15 Gibofsky A. Epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis: a synopsis. *Am J Manag Care* 2015;**20**:S128-135.

16 Zaccardelli A, Friedlander HM, Ford JA, *et al.* Potential of lifestyle changes for reducing the risk of developing rheumatoid arthritis: is an ounce of prevention worth a pound of cure? *Clin Ther* 2019;**41**:1323–45. doi:10.1016/j.clinthera.2019.04.021

17 Hair MJH de, Landewé RBM, Sande MGH van de, *et al.* Smoking and overweight determine the likelihood of developing rheumatoid arthritis. *Ann Rheum Dis* 2013;**72**:1654–8. doi:10.1136/annrheumdis-2012-202254

18 Aletaha D, Neogi T, Silman AJ, *et al.* 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;**62**:2569–81. doi:10.1002/art.27584

19 Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24. doi:10.1002/art.1780310302

20 Kyburz D, Finckh A. The importance of early treatment for the prognosis of rheumatoid arthritis. *Swiss Med Wkly* 2013;**143**:w13865. doi:10.4414/smw.2013.13865

21 Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. *Lancet Lond Engl* 2017;**389**:2338–48. doi:10.1016/S0140-6736(17)31491-5

22 England BR, Tiong BK, Bergman MJ, *et al.* 2019 Update of the American College of Rheumatology recommended rheumatoid arthritis disease activity measures. *Arthritis Care Res* 2019;**71**:1540–55. doi:10.1002/acr.24042

23 American College of Rheumatology. Rheumatoid Arthritis (RA). Rheumatology.org. 2020.https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Rheumatoid-Arthritis (accessed 18 Jan 2021).

24 Kirkham JJ, Boers M, Tugwell P, *et al.* Outcome measures in rheumatoid arthritis randomised trials over the last 50 years. *Trials* 2013;**14**:324. doi:10.1186/1745-6215-14-324

25 Boers M, Tugwell P, Felson DT, *et al.* World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. *J Rheumatol Suppl* 1994;**41**:86–9.

26 Dudler J, Möller B, Michel BA, *et al.* Biologics in rheumatoid arthritis: recommendations for Swiss practice. *Swiss Med Wkly* 2011;**141**:w13189. doi:10.4414/smw.2011.13189

27 Aletaha D, Smolen JS. The Simplified Disease Activity Index and Clinical Disease Activity Index to monitor patients in standard clinical care. *Rheum Dis Clin N Am* 2009;**35**:759–72. doi:10.1016/j.rdc.2009.10.006

28 Solomon DH, Bitton A, Katz JN, *et al.* Treat to target in rheumatoid arthritis: fact, fiction or hypothesis? *Arthritis Rheumatol* 2014;**66**:775–82. doi:10.1002/art.38323

29 Wolfe F, Michaud K, Pincus T. A composite disease activity scale for clinical practice, observational studies, and clinical trials: the patient activity scale (PAS/PAS-II). *J Rheumatol* 2005;**32**:2410–5.

30 Pincus T, Yazici Y, Bergman MJ. RAPID3, an index to assess and monitor patients with rheumatoid arthritis, without formal joint counts: similar results to DAS28 and CDAI in clinical trials and clinical care. *Rheum Dis Clin North Am* 2009;**35**:773–8, viii. doi:10.1016/j.rdc.2009.10.008

31 Pincus T, Swearingen CJ, Bergman MJ, *et al.* RAPID3 (Routine Assessment of Patient Index Data) on an MDHAQ (Multidimensional Health Assessment Questionnaire): agreement with DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) activity categories, scored in five versus more than ninety seconds. *Arthritis Care Res* 2010;**62**:181–9. doi:10.1002/acr.20066

32 Gossec L, Dougados M, Dixon W. Patient-reported outcomes as end points in clinical trials in rheumatoid arthritis. *RMD Open* 2015;**1**:e000019. doi:10.1136/rmdopen-2014-000019

33 Orbai A-M, Bingham CO. Patient reported outcomes in rheumatoid arthritis clinical trials. *Curr Rheumatol Rep* 2015;**17**:501. doi:10.1007/s11926-015-0501-8

34 van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998;**41**:1845–50. doi:10.1002/1529-0131(199810)41:10<1845::AID-ART17>3.0.CO;2-K

35 Felson DT, Anderson JJ, Lange ML, *et al.* Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? *Arthritis Rheum* 1998;**41**:1564–70. doi:10.1002/1529-0131(199809)41:9<1564::AID-ART6>3.0.CO;2-M

36 Salaffi F, Carotti M, Beci G, *et al.* Radiographic scoring methods in rheumatoid arthritis and psoriatic arthritis. *Radiol Med (Torino)* 2019;**124**:1071–86. doi:10.1007/s11547-019-01001-3

37 Farheen K, Agarwal SK. Assessment of disease activity and treatment outcomes in rheumatoid arthritis. *J Manag Care Spec Pharm* 2011;**17**:S09-13. doi:10.18553/jmcp.2011.17.s9-b.s09

38 Scott DL, Houssien DA. Joint assessment in rheumatoid arthritis. *Br J Rheumatol* 1996;**35**:14–8. doi:10.1093/rheumatology/35.suppl_2.14

39 Nikiphorou E, Radner H, Chatzidionysiou K, *et al.* Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. *Arthritis Res Ther* 2016;**18**:251. doi:10.1186/s13075-016-1151-6

40 Rifbjerg-Madsen S, Christensen AW, Boesen M, *et al.* The course of pain hypersensitivity according to painDETECT in patients with rheumatoid arthritis initiating treatment: results from the prospective FRAME-cohort study. *Arthritis Res Ther* 2018;**20**:105–105. doi:10.1186/s13075-018-1581-4

41 Choy T, Bykerk VP, Boire G, *et al.* Physician global assessment at 3 months is strongly predictive of remission at 12 months in early rheumatoid arthritis: results from the CATCH cohort. *Rheumatology* 2014;**53**:482–90. doi:10.1093/rheumatology/ket366

42 Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). *Arthritis Care Res* 2011;**63**:S4–13. doi:10.1002/acr.20620

43 Aletaha D, Ward MM, Machold KP, *et al.* Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum* 2005;**52**:2625–36. doi:10.1002/art.21235

44 van der Heijde DM, van't Hof MA, van Riel PL, *et al.* Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990;**49**:916–20. doi:10.1136/ard.49.11.916

45 Smolen JS, Breedveld FC, Schiff MH, *et al.* A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology* 2003;**42**:244–57. doi:10.1093/rheumatology/keg072

46 Felson DT, Smolen JS, Wells G, *et al.* American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011;**63**:573–86. doi:10.1002/art.30129

47 Felson DT, Anderson JJ, Boers M, *et al.* The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials: the Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum* 1993;**36**:729–40. doi:10.1002/art.1780360601

48 Felson DT, Anderson JJ, Boers M, *et al.* American College of Rheumatology: preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:727–35. doi:10.1002/art.1780380602

49 Santos EJF, Duarte C, da Silva JAP, *et al.* The impact of fatigue in rheumatoid arthritis and the challenges of its assessment. *Rheumatology* 2019;**58**:v3–9. doi:10.1093/rheumatology/kez351

50 Singh JA, Saag KG, Bridges SL, *et al.* 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res* 2016;**68**:1–25. doi:10.1002/acr.22783

51 Demoruelle MK, Deane KD. Treatment strategies in early rheumatoid arthritis and prevention of rheumatoid arthritis. *Curr Rheumatol Rep* 2012;**14**:472–80. doi:10.1007/s11926-012-0275-1

52 Breedveld FC. Current and future management approaches for rheumatoid arthritis. *Arthritis Res* 2002;**4**:S16–21. doi:10.1186/ar548

53 Schneider M, Baseler G, Funken O, *et al.* Management der frühen rheumatoiden Arthritis. Deutsche Gesellschaft für Rheumatologie 2019. https://www.awmf.org/uploads/tx_szleitlinien/060-002l_S3_Fruehe_Rheumatoide-Arthritis-Management_2019-12_01.pdf (accessed 25 Mar 2020).

54 SGR. Behandlungsempfehlungen der SGR. Schweiz. Ges. Für Rheumatol. https://www.rheuma-net.ch/de/fachinformationen/behandlungsempfehlungen (accessed 30 Mar 2020).

55 Bullock J, Rizvi SAA, Saleh AM, *et al.* Rheumatoid arthritis: a brief overview of the treatment. *Med Princ Pract* 2018;**27**:501–7. doi:10.1159/000493390

56 Kyburz D, Gabay C, Michel BA, *et al.* The long-term impact of early treatment of rheumatoid arthritis on radiographic progression: a population-based cohort study. *Rheumatology* 2011;**50**:1106–10. doi:10.1093/rheumatology/keq424

57 Radner H, Aletaha D. Anti-TNF in rheumatoid arthritis: an overview. *Wien Med Wochenschr* 2015;**165**:3–9. doi:10.1007/s10354-015-0344-y

58 Christie A, Jamtvedt G, Dahm KT, *et al.* Effectiveness of nonpharmacological and nonsurgical interventions for patients with rheumatoid arthritis: an overview of systematic reviews. *Phys Ther* 2007;**87**:1697–715. doi:10.2522/ptj.20070039

59 Zink A, Minden K, List SM. Entzündlich rheumatische Erkrankungen - Themenheft. Robert-Koch-Institut 2010. http://www.gbe-bund.de/gbe10/abrechnung.prc_abr_test_logon?p_uid=gast&p_aid=0&p_knoten=FID&p_sprache=D&p_suchstring=12929 (accessed 25 Mar 2020).

60 Rheumaliga Schweiz. Arthritis. rheumaliga.ch. https://www.rheumaliga.ch/rheuma-von-a-z/arthritis (accessed 31 Mar 2020).

61 Uhlig T, Moe RH, Kvien TK. The burden of disease in rheumatoid arthritis. *PharmacoEconomics* 2014;**32**:841–51. doi:10.1007/s40273-014-0174-6

62 Hunter TM, Boytsov NN, Zhang X, *et al.* Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014. *Rheumatol Int* 2017;**37**:1551–7. doi:10.1007/s00296-017-3726-1

63 Safiri S, Kolahi AA, Hoy D, *et al.* Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. *Ann Rheum Dis* 2019;**78**:1463–71. doi:10.1136/annrheumdis-2019-215920

64 Doran MF, Pond GR, Crowson CS, *et al.* Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. *Arthritis Rheum* 2002;**46**:625–31. doi:10.1002/art.509

65 Crowson CS, Matteson EL, Myasoedova E, *et al.* The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis Rheum* 2011;**63**:633–9. doi:10.1002/art.30155

66 Listing J, Kekow J, Manger B, *et al.* Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. *Ann Rheum Dis* 2015;**74**:415–21. doi:10.1136/annrheumdis-2013-204021

67 van den Hoek J, Boshuizen HC, Roorda LD, *et al.* Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. *Rheumatol Int* 2017;**37**:487–93. doi:10.1007/s00296-016-3638-5

68 Boonen A, Severens JL. The burden of illness of rheumatoid arthritis. *Clin Rheumatol* 2011;**30 Suppl 1**:S3-8. doi:10.1007/s10067-010-1634-9

69 Chen C-I, Wang L, Wei W, *et al.* Burden of rheumatoid arthritis among US Medicare population: co-morbidities, health-care resource utilization and costs. *Rheumatol Adv Pract* 2018;**2**. doi:10.1093/rap/rky005

70 England BR, Thiele GM, Anderson DR, *et al.* Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. *BMJ* 2018;**361**:k1036. doi:10.1136/bmj.k1036

71 Dixon WG, Hyrich KL, Watson KD, *et al.* Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis* 2010;**69**:522–8. doi:10.1136/ard.2009.118935

72 Costello R, David T, Jani M. Impact of Adverse Events Associated With Medications in the Treatment and Prevention of Rheumatoid Arthritis. *Clin Ther* 2019;**41**:1376–96. doi:10.1016/j.clinthera.2019.04.030

73 Matcham F, Scott IC, Rayner L, *et al.* The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2014;**44**:123–30. doi:10.1016/j.semarthrit.2014.05.001

74 Kostova Z, Caiata-Zufferey M, Schulz PJ. The process of acceptance among rheumatoid arthritis patients in Switzerland: a qualitative study. *Pain Res Manag* 19;**19**:168472. doi:https://doi.org/10.1155/2014/168472

75 Wieser S, Tomonaga Y, Riguzzi M, *et al.* Die Kosten der nichtübertragbaren Krankheiten in der Schweiz: Schlussbericht. ZHAW Zürcher Hochschule für Angewandte Wissenschaften, Polynomics, Universität Zürich 2014. https://www.bag.admin.ch/dam/bag/de/dokumente/npp/forschungsberichte/forschungsberichte-ncd/kosten-ncd-in-der-schweiz.pdf.download.pdf/Schlussbericht%20COI%20NCDs%20in%20CH%202014%2007%2021.pdf (accessed 4 Apr 2020).

76 Hsieh P-H, Wu O, Geue C, *et al.* Economic burden of rheumatoid arthritis: a systematic review of literature in biologic era. *Ann Rheum Dis* 2020;**79**:771–7. doi:10.1136/annrheumdis-2019-216243

77 Sokka T, Kautiainen H, Pincus T, *et al.* Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. *Arthritis Res Ther* 2010;**12**:R42. doi:10.1186/ar2951

78 Morrow T, Felcone LH. Defining the difference: what makes biologics unique. *Biotechnol Healthc* 2004;**1**:24–9.

79 Ramanan S, Grampp G. Drift, evolution, and divergence in biologics and biosimilars manufacturing. *BioDrugs* 2014;**28**:363–72. doi:10.1007/s40259-014-0088-z

80 Ebbers HC, Fehrmann B, Ottosen M, *et al.* Batch-to-batch consistency of SB4 and SB2, etanercept and infliximab biosimilars. *BioDrugs* 2020;**34**:225–33. doi:10.1007/s40259-019-00402-0

81 Planinc A, Dejaegher B, Heyden YV, *et al.* Batch-to-batch N-glycosylation study of infliximab, trastuzumab and bevacizumab, and stability study of bevacizumab. *Eur J Hosp Pharm* 2017;**24**:286–92. doi:10.1136/ejhpharm-2016-001022

82 Weise M, Kurki P, Wolff-Holz E, *et al.* Biosimilars: the science of extrapolation. *Blood* 2014;**124**:3191–6. doi:10.1182/blood-2014-06-583617

83 Duivelshof BL, Jiskoot W, Beck A, *et al.* Glycosylation of biosimilars: recent advances in analytical characterization and clinical implications. *Anal Chim Acta* 2019;**1089**:1–18. doi:10.1016/j.aca.2019.08.044

84 Dutta B, Huys I, Vulto AG, *et al.* Identifying key benefits in European off-patent biologics and biosimilar markets: it is not only about price! *BioDrugs* 2020;**34**:159–70. doi:10.1007/s40259-019-00395-w

85 Buss NA, Henderson SJ, McFarlane M, *et al.* Monoclonal antibody therapeutics: history and future. *Curr Opin Pharmacol* 2012;**12**:615–22. doi:10.1016/j.coph.2012.08.001

86 Maini RN, Feldmann M. How does infliximab work in rheumatoid arthritis? *Arthritis Res* 2002;**4**:S22–8. doi:10.1186/ar549

87 HCI Solutions AG. REMICADE Trockensub 100 mg. compendium.ch. https://compendium.ch/product/81983-remicade-trockensub-100-mg (accessed 4 Apr 2020).

88 Flendrie M, Creemers MCW, van Riel PLCM. Titration of infliximab treatment in rheumatoid arthritis patients based on response patterns. *Rheumatology* 2007;**46**:146–9. doi:10.1093/rheumatology/kel173

89 Fatima R, Bittar K, Aziz M. Infliximab. In: *StatPearls*. StatPearls Publishing 2020. Treasure Island, FL.http://www.ncbi.nlm.nih.gov/books/NBK500021/ (accessed 4 Apr 2020).

90 Minozzi S, Bonovas S, Lytras T, *et al.* Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2016;**15**:11–34. doi:10.1080/14740338.2016.1240783

91 Blair HA, Deeks ED. Infliximab biosimilar (CT-P13; infliximab-dyyb): a review in autoimmune inflammatory diseases. *BioDrugs* 2016;**30**:469–80. doi:10.1007/s40259-016-0193-2

92 Bundesamt für Gesundheit. Spezialtätenliste - Substanz - Infliximab. spezialitätenliste.ch. 2021.http://www.spezialitätenliste.ch/ (accessed 18 Jan 2021).

93 Harrington R, Al Nokhatha SA, Conway R. JAK Inhibitors in Rheumatoid Arthritis: An Evidence-Based Review on the Emerging Clinical Data. *J Inflamm Res* 2020;**13**:519–31. doi:10.2147/JIR.S219586

94 Schneider R, Schur N, Reinau D, *et al.* Helsana Arneimittelreport für die Schweiz 2018. Helsana 2018. https://www.helsana.ch/en/helsana-group/about-our-company/health-sciences/drug-report

95 Schneider R, Schur N, Reinau D, *et al.* Helsana-Arzneimittelreport für die Schweiz 2019. Helsana 2019. https://www.helsana.ch/en/helsana-group/about-our-company/health-sciences/drug-report (accessed 10 Feb 2020).

96 Lamb YN, Deeks ED. Sarilumab: a review in moderate to severe rheumatoid arthritis. *Drugs* 2018;**78**:929–40. doi:10.1007/s40265-018-0929-z

97 Rubbert-Roth A, Furst DE, Nebesky JM, *et al.* A review of recent advances using tocilizumab in the treatment of rheumatic diseases. *Rheumatol Ther* 2018;**5**:21–42. doi:10.1007/s40744-018-0102-x

98 Dubois EA, Cohen AF. Abatacept. *Br J Clin Pharmacol* 2009;**68**:480–1. doi:10.1111/j.1365-2125.2009.03502.x

99 Taylor PC. Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. *Rheumatology* 2019;**58**:i17–26. doi:10.1093/rheumatology/key225

100 Swissmedic. Lists and directories. https://www.swissmedic.ch/swissmedic/en/home/services/listen_neu.html (accessed 18 Jan 2021).

101 Revicki DA, Frank L. Pharmacoeconomic evaluation in the real world: effectiveness versus efficacy studies. *PharmacoEconomics* 1999;**15**:423–34. doi:10.2165/00019053-199915050-00001

102 Smolen JS, Choe J-Y, Prodanovic N, *et al.* Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study. *Ann Rheum Dis* 2018;**77**:234–40. doi:10.1136/annrheumdis-2017-211741

103 Isakov L, Jin B, Jacobs IA. Statistical primer on biosimilar clinical development. *Am J Ther* 2016;**23**:e1903–10. doi:10.1097/MJT.0000000000000391

104 McKinnon RA, Cook M, Liauw W, *et al.* Biosimilarity and interchangeability: principles and evidence: a systematic review. *BioDrugs* 2018;**32**:27–52. doi:10.1007/s40259-017-0256-z

105 EMA. ICH E2A Clinical safety data management: definitions and standards for expedited reporting. European Medicines Agency 1995. https://www.ema.europa.eu/en/ich-e2a-clinical-safety-data-management-definitions-standards-expedited-reporting (accessed 6 Apr 2020).

106 Drummond MF, Sculpher MJ, Claxton K, *et al. Methods for the economic evaluation of health care programmes*. Fourth Edition. Oxford University Press 2015.

107 Stich AK, Mozygemba K, Lysdahl KB, *et al.* Methods assessing sociocultural aspects of health technologies: results of a literature review. *Int J Technol Assess Health Care* 2019;:1–7. doi:10.1017/S0266462319000102

108 EUnetHTA Joint Action 2, Work Package 8. HTA Core Model version 3.0 for the full assessment of diagnostic technologies, medical and surgical interventions, pharmaceuticals and screening technologies. 2016. https://eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf (accessed 15 Nov 2019).

109 Lee A, Skött LS, Hansen HP. Organizational and patient-related assessments in HTAs: state of the art. *Int J Technol Assess Health Care* 2009;**25**:530–6. doi:10.1017/S0266462309990456

110 Widrig D. *Health Technology Assessment*. Springer-Verlag 2015.

111 Hofmann BM. Why ethics should be part of health technology assessment. *Int J Technol Assess Health Care* 2008;**24**:423–9. doi:10.1017/S0266462308080550

112 Hofmann B. Toward a procedure for integrating moral issues in health technology assessment. *Int J Technol Assess Health Care* 2005;**21**:312–8. doi:10.1017/S0266462305050415

113 Eichenberger T, Helmle C. Keine direkte oder analoge Anwendung von Art. 52a KVG auf Biosimilars. *Hill* 2014;**166**.

114 Dormuth CR, Fisher A, Carney G. A rapid monitoring plan following a shift in coverage from brand name to biosimilar drugs for rheumatoid arthritis in British Columbia. *Pharmacoepidemiol Drug Saf* Published Online First: 2020. doi:10.1002/pds.4957

115 Moorkens E, Simoens S, Troein P, *et al.* Different policy measures and practices between Swedish counties influence market dynamics: part 1-biosimilar and originator infliximab in the hospital setting. *BioDrugs* 2019;**33**:285–97. doi:10.1007/s40259-019-00345-6

116 Moorkens E, Simoens S, Troein P, *et al.* Different policy measures and practices between Swedish counties influence market dynamics: part 2-biosimilar and originator etanercept in the outpatient setting. *BioDrugs* 2019;**33**:299–306. doi:10.1007/s40259-019-00346-5

117 Wolff-Holz E, Tiitso K, Vleminckx C, *et al.* Evolution of the EU biosimilar framework: past and future. *BioDrugs* 2019;**33**:621–34. doi:10.1007/s40259-019-00377-y

118 Committee for Human Medicinal Products (CHMP). Guideline on similar biological medicinal products. London. European Medicines Agency 2014. https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf (accessed 10 Apr 2020).

119 Rezk MF, Pieper B. To See or NOsee: the debate on the nocebo effect and optimizing the use of biosimilars. *Adv Ther* 2018;**35**:749–53. doi:10.1007/s12325-018-0719-8

120 Tweehuysen L, van den Bemt BJF, van Ingen IL, *et al.* Subjective complaints as the main reason for biosimilar discontinuation after open-label transition from reference infliximab to biosimilar infliximab. *Arthritis Rheumatol* 2018;**70**:60–8. doi:10.1002/art.40324

121 Kohl C, McIntosh EJ, Unger S, *et al.* Online tools supporting the conduct and reporting of systematic reviews and systematic maps: a case study on CADIMA and review of existing tools. *Environ Evid* 2018;**7**:8. doi:10.1186/s13750-018-0115-5

122 Higgins JP, Churchill R, Chandler J, *et al.* Cochrane Handbook for Systematic Reviews of Interventions. Cochrane 2017. Chapter 8: Assessing risk of bias in included studies.

123 Schünemann HJ, Higgins JP, Vist G, *et al.* Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane 2020.

124 Bae S-C, Lee YH. Comparative efficacy and safety of biosimilar-infliximab and originator-infliximab in combination with methotrexate in patients with active rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Int J Rheum Dis* 2018;**21**:922–9. doi:10.1111/1756-185X.13305

125 Komaki Y, Yamada A, Komaki F, *et al.* Efficacy, safety and pharmacokinetics of biosimilars of anti-tumor necrosis factor-α agents in rheumatic diseases: a systematic review and meta-analysis. *J Autoimmun* 2017;**79**:4–16. doi:10.1016/j.jaut.2017.02.003

126 Baji P, Péntek M, Czirják L, *et al.* Efficacy and safety of infliximab-biosimilar compared to other biological drugs in rheumatoid arthritis: a mixed treatment comparison. *Eur J Health Econ* 2014;**15**:S53-64. doi:10.1007/s10198-014-0594-4

127 Borenstein M, Hedges LV, Higgins JPT, *et al.* A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;**1**:97–111. doi:10.1002/jrsm.12

128 Harris RJ, Deeks JJ, Altman DG, *et al.* Metan: Fixed- and Random-Effects Meta-Analysis. *Stata J* 2008;**8**:3–28. doi:10.1177/1536867X0800800102

129 StataCorp. *Stata Statistical Software*. StataCorp LLC 2017.

130 Borenstein M, Hedges LV, Higgins JPT, *et al.* A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;**1**:97–111. doi:10.1002/jrsm.12

131 Higgins JPT, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60.

132 Egger M, Davey Smith G, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.

133 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. *PLOS Med* 2009;**6**:e1000097. doi:10.1371/journal.pmed.1000097

134 Alten R, Batko B, Hala T, *et al.* Randomised, double-blind, phase III study comparing the infliximab biosimilar, PF-06438179/GP1111, with reference infliximab: efficacy, safety and immunogenicity from week 30 to week 54. *RMD Open* 2019;**5**:e000876. doi:10.1136/rmdopen-2018-000876

135 Cohen SB, Alten R, Kameda H, *et al.* A randomized controlled trial comparing PF-06438179/GP1111 (an infliximab biosimilar) and infliximab reference product for treatment of moderate to severe active rheumatoid arthritis despite methotrexate therapy. *Arthritis Res Ther* 2018;**20**:155. doi:10.1186/s13075-018-1646-4

136 Choe J-Y, Prodanovic N, Niebrzydowski J, *et al.* A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;**76**:58–64. doi:10.1136/annrheumdis-2015-207764

137 Smolen JS, Choe J-Y, Prodanovic N, *et al.* Comparing biosimilar SB2 with reference infliximab after 54 weeks of a double-blind trial: clinical, structural and safety results. *Rheumatology* 2017;**56**:1771–9. doi:10.1093/rheumatology/kex254

138 Takeuchi T, Yamanaka H, Tanaka Y, *et al.* Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 2015;**25**:817–24. doi:10.3109/14397595.2015.1022297

139 Genovese MC, Sanchez-Burson J, Oh M, *et al.* Comparative clinical efficacy and safety of the proposed biosimilar ABP 710 with infliximab reference product in patients with rheumatoid arthritis. *Arthritis Res Ther* 2020;**22**:60. doi:10.1186/s13075-020-2142-1

140 Boone NW, Liu L, Romberg-Camps MJ, *et al.* The nocebo effect challenges the non-medical infliximab switch in practice. *Eur J Clin Pharmacol* 2018;**74**:655–61. doi:10.1007/s00228-018-2418-4

141 Avouac J, Moltó A, Abitbol V, *et al.* Systematic switch from innovator infliximab to biosimilar infliximab in inflammatory chronic diseases in daily clinical practice: the experience of Cochin University Hospital, Paris, France. *Semin Arthritis Rheum* 2018;**47**:741–8. doi:10.1016/j.semarthrit.2017.10.002

142 Glintborg B, Kringelbach T, Bolstad N, *et al.* Drug concentrations and anti-drug antibodies during treatment with biosimilar infliximab (CT-P13) in routine care. *Scand J Rheumatol* 2018;**47**:418–21. doi:10.1080/03009742.2017.1376110

143 Glintborg B, Sørensen IJ, Loft AG, *et al.* A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. *Ann Rheum Dis* 2017;**76**:1426–31. doi:10.1136/annrheumdis-2016-210742

144 Grøn KL, Glintborg B, Nørgaard M, *et al.* Comparative effectiveness of certolizumab pegol, abatacept, and biosimilar infliximab in patients with rheumatoid arthritis treated in routine care: observational data from the Danish DANBIO registry emulating a randomized trial. *Arthritis Rheumatol* 2019;**71**:1997–2004. doi:10.1002/art.41031

145 Holroyd CR, Parker L, Bennett S, *et al.* Switching to biosimilar infliximab: real world data in patients with severe inflammatory arthritis. *Clin Exp Rheumatol* 2018;**36**:171–2.

146 Layegh Z, Ruwaard J, Hebing RCF, *et al.* Efficacious transition from reference infliximab to biosimilar infliximab in clinical practice. *Int J Rheum Dis* 2019;**22**:869–73. doi:10.1111/1756-185X.13512

147 Nikiphorou E, Kautiainen H, Hannonen P, *et al.* Clinical effectiveness of CT-P13 (infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease: report of clinical experience based on prospective observational data. *Expert Opin Biol Ther* 2015;**15**:1677–83. doi:10.1517/14712598.2015.1103733

148 Nikiphorou E, Hannonen P, Asikainen J, *et al.* Survival and safety of infliximab bio-original and infliximab biosimilar (CT-P13) in usual rheumatology care. *Clin Exp Rheumatol* 2019;**37**:55–9.

149 Scavone C, Sessa M, Clementi E, *et al.* Real world data on the utilization pattern and safety profile of infliximab originator versus biosimilars in Italy: a multiregional study. *BioDrugs* 2018;**32**:607–17. doi:10.1007/s40259-018-0313-2

150 Scherlinger M, Germain V, Labadie C, *et al.* Switching from originator infliximab to biosimilar CT-P13 in real-life: the weight of patient acceptance. *Joint Bone Spine* 2018;**85**:561–7. doi:10.1016/j.jbspin.2017.10.003

151 Schmitz EMH, Benoy-De Keuster S, Meier AJL, *et al.* Therapeutic drug monitoring (TDM) as a tool in the switch from infliximab innovator to biosimilar in rheumatic patients: results of a 12-month observational prospective cohort study. *Clin Rheumatol* 2017;**36**:2129–34. doi:10.1007/s10067-017-3686-6

152 Vergara-Dangond C, Sáez Belló M, Climente Martí M, *et al.* Effectiveness and safety of switching from innovator infliximab to biosimilar CT-P13 in inflammatory rheumatic diseases: a real-world case study. *Drugs RD* 2017;**17**:481–5. doi:10.1007/s40268-017-0194-8

153 Dutcher SK, Fazio-Eynullayeva E, Eworuke E, *et al.* Understanding utilization patterns of biologics and biosimilars in the United States to support postmarketing studies of safety and effectiveness. *Pharmacoepidemiol Drug Saf* 2020;**29**:786–95. doi:10.1002/pds.4908

154 Fisher A, Kim JD, Dormuth CR. Rapid monitoring of health services utilization following a shift in coverage from brand name to biosimilar drugs in British Columbia—An interim report. *Pharmacoepidemiol Drug Saf* 2020;**29**:803–10. doi:10.1002/pds.5008

155 Saxby K, Sanghvi S, Bodalia PN, *et al.* A novel approach to support implementation of biosimilars within a UK tertiary hospital. *Br J Clin Pharmacol* 2020;**86**:23–8. doi:10.1111/bcp.14150

156 Takeuchi T, Yamanaka H, Tanaka Y, *et al.* Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 2015;**25**:817–24. doi:10.3109/14397595.2015.1022297

157 Yoo D.H., Racewicz A., Brzezicki J., *et al.* A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. *Arthritis Res Ther* 2016;**18**. doi:10.1186/s13075-016-0981-6

158 Evers S, Goossens M, de Vet H, *et al.* Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5.

159 Aladul MI, Fitzpatrick RW, Chapman SR. The effect of new biosimilars in rheumatology and gastroenterology specialities on UK healthcare budgets: results of a budget impact analysis. *Res Soc Adm Pharm* 2019;**15**:310–7. doi:10.1016/j.sapharm.2018.05.009

160 Aladul MI, Fitzpatrick RW, Chapman SR. Impact of infliximab and etanercept biosimilars on biological disease-modifying antirheumatic drugs utilisation and NHS budget in the UK. *BioDrugs* 2017;**31**:533–44. doi:10.1007/s40259-017-0252-3

161 Beck M, Michel B, Rybarczyk-Vigouret M-C, *et al.* Biosimilar infliximab for the management of rheumatoid arthritis in France: what are the expected savings? *Eur J Hosp Pharm* 2017;**24**:85–90. doi:10.1136/ejhpharm-2016-000904

162 Curtis JR, Xie F, Kay J, *et al.* Will savings from biosimilars offset increased costs related to dose escalation? A comparison of infliximab and golimumab for rheumatoid arthritis. *Arthritis Res Ther* 2019;**21**:285. doi:10.1186/s13075-019-2022-8

163 Gibofsky A, Skup M, Yang M, *et al.* Short-term costs associated with non-medical switching in autoimmune conditions. *Clin Exp Rheumatol* 2019;**37**:97–105.

164 Jha A, Upton A, Dunlop WCN, *et al.* The budget impact of biosimilar infliximab (Remsima®) for the treatment of autoimmune diseases in five European countries. *Adv Ther* 2015;**32**:742–56. doi:10.1007/s12325-015-0233-1

165 Kanters TA, Stevanovic J, Huys I, *et al.* Adoption of biosimilar infliximab for rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel diseases in the EU5: a budget impact analysis using a Delphi panel. *Front Pharmacol* 2017;**8**:322. doi:10.3389/fphar.2017.00322

166 Lucioni C, Mazzi S, Caporali R. Budget impact analysis of infliximab biosimilar: the Italian scenery. *Glob Reg Health Technol Assess* Published Online First: 7 October 2015. doi:10.5301/GRHTA.5000194

167 Yazdany J, Dudley RA, Lin GA, *et al.* Out-of-pocket costs for infliximab and its biosimilar for rheumatoid arthritis under Medicare Part D. *JAMA* 2018;**320**:931–3. doi:10.1001/jama.2018.7316

168 Mansell K, Bhimji H, Eurich D, *et al.* Potential cost-savings from the use of the biosimilars filgrastim, infliximab and insulin glargine in Canada: a retrospective analysis. *BMC Health Serv Res* 2019;**19**:827. doi:10.1186/s12913-019-4680-2

169 Crosby M, Tadrous M, Gomes T. Potential Cost Implications of Mandatory Non-Medical Switching Policies for Biologics for Rheumatic Conditions and Inflammatory Bowel Disease in Canada. *Clin Pharmacol Ther* 2020;:cpt.2042. doi:10.1002/cpt.2042

170 Ghabri S, Binard A, Pers Y-M, *et al.* Economic Evaluation of Sequences of Biological Treatments for Patients With Moderate-to-Severe Rheumatoid Arthritis and Inadequate Response or Intolerance to Methotrexate in France. *Value Health J Int Soc Pharmacoeconomics Outcomes Res* 2020;**23**:461–70. doi:10.1016/j.jval.2019.12.003

171 Glintborg B, Sørensen J, Hetland ML. Does a mandatory non-medical switch from originator to biosimilar infliximab lead to increased use of outpatient healthcare resources? A register-based study in patients with inflammatory arthritis. *RMD Open* 2018;**4**:e000710. doi:10.1136/rmdopen-2018-000710

172 Sagili KD, Muniyandi M, Nilgiriwala KS, *et al.* Cost-effectiveness of GeneXpert and LED-FM for diagnosis of pulmonary tuberculosis: A systematic review. *PloS One* 2018;**13**:e0205233. doi:10.1371/journal.pone.0205233

173 Stewart A, Aubrey P, Belsey J. Addressing the health technology assessment of biosimilar pharmaceuticals. *Curr Med Res Opin* 2010;**26**:2119–26. doi:10.1185/03007995.2010.505137

174 Simoens S, Jacobs I, Popovian R, *et al.* Assessing the value of biosimilars: a review of the role of budget impact analysis. *PharmacoEconomics* 2017;**35**:1047–62. doi:10.1007/s40273-017-0529-x

175 Moorkens E, Broux H, Huys I, *et al.* Economic evaluation of biosimilars for reimbursement purposes - what, when, how? *J Mark Access Health Policy* 2020;**8**:1739509. doi:10.1080/20016689.2020.1739509

176 Stevenson M, Archer R, Tosh J, *et al.* Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. *Health Technol Assess* 2016;**20**:1–610. doi:10.3310/hta20350

177 Swiss Clinical Quality Management Foundation (SCQM) in Rheumatic Diseases. Prevalences of Treatment with Infliximab in RA Patients. Unpublished data from the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) Foundation. SCQM 2021.

178 Uitz E, Fransen J, Langenegger T, *et al.* Clinical quality management in rheumatoid arthritis: putting theory into practice. Swiss Clinical Quality Management in Rheumatoid Arthritis. *Rheumatol Oxf Engl* 2000;**39**:542–9. doi:10.1093/rheumatology/39.5.542

179 Jansen JP, Incerti D. The IVI-RA model. https://innovationvalueinitiative.github.io/IVI-RA/ (accessed 16 Apr 2020).

180 Guyot P, Ades AE, Ouwens MJNM, *et al.* Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;**12**:9. doi:10.1186/1471-2288-12-9

181 Bundesamt für Statistik. Vollständige jährliche Sterbetafel (Frauen), 2013-2019 - 2013-2019 | Tabelle. Bundesamt Für Stat. 2020./content/bfs/de/home/statistiken/bevoelkerung/geburten-todesfaelle/lebenserwartung.assetdetail.14387086.html (accessed 27 Jan 2021).

182 Bundesamt für Statistik. Vollständige jährliche Sterbetafel (Männer), 2013-2019 - 2013-2019 | Tabelle. Bundesamt Für Stat. 2020./content/bfs/de/home/statistiken/bevoelkerung/geburten-todesfaelle/lebenserwartung.assetdetail.14387068.html (accessed 27 Jan 2021).

183 Toledano E, Candelas G, Rosales Z, *et al.* A meta-analysis of mortality in rheumatic diseases. *Reumatol Clínica* 2012;**8**:334–41. doi:10.1016/j.reuma.2012.05.006

184 Dadoun S, Zeboulon-Ktorza N, Combescure C, *et al.* Mortality in rheumatoid arthritis over the last fifty years: Systematic review and meta-analysis. *Joint Bone Spine* 2013;**80**:29–33. doi:10.1016/j.jbspin.2012.02.005

185 Houge IS, Hoff M, Thomas R, *et al.* Mortality is increased in patients with rheumatoid arthritis or diabetes compared to the general population – the Nord-Trøndelag Health Study. *Sci Rep* 2020;**10**:3593. doi:10.1038/s41598-020-60621-2

186 Løppenthin K, Esbensen BA, Østergaard M, *et al.* Morbidity and mortality in patients with rheumatoid arthritis compared with an age- and sex-matched control population: A nationwide register study. *J Comorbidity* 2019;**9**:2235042X19853484. doi:10.1177/2235042X19853484

187 Listing J, Kekow J, Manger B, *et al.* Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. *Ann Rheum Dis* 2015;**74**:415–21. doi:10.1136/annrheumdis-2013-204021

188 Poiroux L, Allanore Y, Kahan A, *et al.* All-cause Mortality Associated with TNF-α Inhibitors in Rheumatoid Arthritis: A Meta-Analysis of Randomized Controlled Trials. *Am J Med* 2015;**128**:1367-1373.e1. doi:10.1016/j.amjmed.2015.07.020

189 Simard JF, Neovius M, Askling J. Mortality rates in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: Drug-specific comparisons in the Swedish Biologics Register. *Arthritis Rheum* 2012;**64**:3502–10. doi:https://doi.org/10.1002/art.34582

190 Bundesamt für Gesundheit. Spezialitätenliste (SL) - Übersicht. 2021.http://www.xn--spezialittenliste-yqb.ch/ (accessed 18 Jan 2021).

191 FMH. TARMED: Tarifbrowser und Datenbank. FMH. https://www.fmh.ch/themen/ambulante-tarife/tarmed-tarifbrowser-datenbank.cfm (accessed 27 Jan 2021).

192 Ingenieurbüro S. Möckli. Taxpunktwerte Tarmed. https://eligo.ch/Tarmed-Taxpunktwerte.html (accessed 26 Jan 2021).

193 Bundesamt für Gesundheit. Analysenliste (AL). https://www.bag.admin.ch/bag/de/home/versicherungen/krankenversicherung/krankenversicherung-leistungen-tarife/Analysenliste.html (accessed 27 Jan 2021).

194 Glintborg B, Ibsen R, Bilbo REQ, *et al.* Does a mandatory non-medical switch from originator to biosimilar etanercept lead to increase in healthcare use and costs? A Danish register-based study of patients with inflammatory arthritis. *RMD Open* 2019;**5**:e001016. doi:10.1136/rmdopen-2019-001016

195 Bundesamt für Statistik. Ständige Wohnbevölkerung nach Alter, Geschlecht und Staatsangehörigkeitskategorie, 2010-2019 - 2010-2019 | Tabelle. Bundesamt Für Stat. 2020./content/bfs/de/home/statistiken/kataloge-datenbanken.assetdetail.13707177.html (accessed 27 Jan 2021).

196 Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States. Institute for Health Metrics and Evaluation (IHME) 2020. http://ghdx.healthdata.org/gbd-results-tool

197 Biétry F, Schur N, Reinau D, *et al.* Helsana-Arzneimittelreport für die Schweiz 2016. Helsana 2016. https://www.helsana.ch/docs/arzneimittelreport-2016.pdf (accessed 4 Dec 2019).

198 Schneider R, Schur N, Reinau D, *et al.* Helsana-Arzneimittelreport für die Schweiz 2017. Helsana 2017. https://www.helsana.ch/docs/arzneimittelreport-2017.pdf (accessed 10 Feb 2020).

199 Pipalava P, Patel R, Mehta M, *et al.* An update on the animal studies conducted for biosimilar approvals: regulatory requirement vs actual scenario. *Regul Toxicol Pharmacol* 2019;**107**:104415. doi:10.1016/j.yrtph.2019.104415

200 Murdoch B, Caulfield T. The law and ethics of switching from biologic to biosimilar in Canada. *J Can Assoc Gastroenterol* 2020;:1–6. doi:10.1093/jcag/gwz043

201 Knoepffler N. [Biosimilars in gastroenterology - how much uncertainly is ethically acceptable?]. *Z Für Gastroenterol* 2016;**54**:1233–6. doi:10.1055/s-0042-118192

202 Burls A, Caron L, Langavant GC de, *et al.* Tackling ethical issues in health technology assessment: a proposed framework. *Int J Technol Assess Health Care* 2011.

203 Droste S, Herrmann-Frank A, Scheibler F, *et al.* Ethical issues in autologous stem cell transplantation (ASCT) in advanced breast cancer: a systematic literature review. *BMC Med Ethics* 2011;**12**:6. doi:10.1186/1472-6939-12-6

204 Hofmann B. Vaksiner mot humant papillomavirus (HPV): etiske aspekter ved innføring av profylaktiske HPVvaksiner. Oslo. Norwegian Knowledge Centre for the Health Services 2008. https://fhi.brage.unit.no/fhi-xmlui/bitstream/handle/11250/2378507/NOKCrapport22_2008.pdf?sequence=1 (accessed 6 Apr 2020).

205 Hofmann B. Ethics in Health Technology Assessments (HTA). Norwegian Knowledge Centre for the Health Services 2008.

206 Schiestl M, Stangler T, Torella C, *et al.* Acceptable changes in quality attributes of glycosylated biopharmaceuticals. *Nat Biotechnol* 2011;**29**:310–2. doi:10.1038/nbt.1839

207 Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. Oxford University Press 2019.

208 Ludwig WD, Dicheva S. [Biosimilars in oncology: a therapeutic alternative to the reference products?]. *Z Gastroenterol* 2016;**54**:1223–9. doi:10.1055/s-0042-117650

209 Kim H, Alten R, Avedano L, *et al.* The future of biosimilars: maximizing benefits across immune-mediated inflammatory diseases. *Drugs* 2020;**80**:99–113. doi:10.1007/s40265-020-01256-5

210 Gordon BG. Vulnerability in Research: Basic Ethical Concepts and General Approach to Review. *Ochsner J* 2020;**20**:34–8. doi:10.31486/toj.19.0079

211 Swissmedic. Fragen und Antworten zur Zulassung von Biosimilars. Bern. Swissmedic 2020. https://www.swissmedic.ch/swissmedic/de/home/services/documents/faq_zl_biosimilar.html (accessed 15 Apr 2020).

212 Wildi A. Art. 52/52a KVG. Basler Kommentar. In: Blechta G-P, Colatrella P, Staffelbach D, *et al.*, eds. *Krankenversicherungsgesetz, Krankenversicherungsaufsichtsgesetz*. Helbing & Lichtenhahn 2020.

213 Schweizerischer Bundesrat. Botschaft zur Änderung des Bundesgesetzes über die Krankenversicherung (Massnahmen zur Kostendämpfung - Paket 1). BBL 2019 2019. https://www.admin.ch/opc/de/federal-gazette/2019/6071.pdf (accessed 1 Apr 2020).

214 Bundesamt für Gesundheit. Änderungen im Handbuch betreffend die Spezialitätenliste (SL) per 1. März 2013. 2013.https://www.swissmedic.ch/dam/swissmedic/de/dokumente/zulassung/zl_hmv_iv/bag_mitteilung_biosimilar.pdf.download.pdf/BAG_Mitteilung_Biosimilars.pdf (accessed 1 Apr 2020).

215 Swissmedic. Wegleitung Arzneimittelinformation für Humanarzneimittel HMV4. Bern. Swissmedic 2020. https://www.swissmedic.ch/dam/swissmedic/de/dokumente/zulassung/zl_hmv_iv/zl000_00_027d_wlarzneimittelinformation.pdf.download.pdf/zl000_00_027d_wlarzneimittelinformation.pdf (accessed 21 Feb 2020).

216 Kobler I, Lenzin G, Liberatore F, *et al.* Biosimilars in der Schweiz: Medizin gegen die steigenden Gesundheitskosten - Ein Expertenbericht des Winterthurer Instituts für Gesundheitsökonomie. Zurich University of Applied Sciences 2020. https://digitalcollection.zhaw.ch/handle/11475/19674 (accessed 15 Apr 2020).

217 Eidgenössische Rekurskommission. VBP 69.97: Entscheid der Eidgenössischen Rekurskommission für Heilmittel vom 12. November 2004 i.S. M. AG [HM 04.070]. 2004. https://entscheidsuche.ch/bund/vpb/69-97.html (accessed 1 Apr 2020).

218 Eichenberger T, Helmle C. Die Wirkstoffverschreibung von biologischen Arzneimitteln in der Schweiz. *Jusletter* 2016.

219 Frahm W, Jansen C, Katzenmeier C, *et al.* Medizin und Standard – Verwerfungen und Perspektiven. *Medizinrecht* 2018;**36**:447–57. doi:10.1007/s00350-018-4957-1

220 Bundesgericht. Regeste: Art. 8 EMRK; Art. 10 BV; Art. 25a VwVG; Art. 64 Abs. 3 KEG; Verfügung über aufsichtsrechtliche Realakte des ENSI (Störfallvorsorge KKW Mühleberg). Bundesgericht 2014. http://relevancy.bger.ch/php/clir/http/index.php?highlight_docid=atf%3A%2F%2F140-II-315%3Ade&lang=de&type=show_document (accessed 1 Apr 2020).

221 Widmer S. Off-label-use in der Schweiz: heilmittelrechtliche Zulässigkeit und Kostenübernahme. *Hill* 2013;**132**.

222 Giger M, Saxer U, Wildi A, *et al. Arzneimittelrecht: eine Wegleitung für die medizinische und pharmazeutische Praxis sowie für Behörden und Versicherer*. Zürich. Schulthess 2013.

223 Druey Just E. Von Sparmassnahmen und Haftungsrisiken. *Schweiz Ärzteztg* 2018;**99**:786–9. doi:10.4414/saez.2018.06690

224 Burri E, Juillerat P, Maillard MH, *et al.* Position statement on the use of biosimilars in inflammatory bowel disease. *Swiss Med Wkly* 2019;**149**. doi:10.4414/smw.2019.20148

225 Moorkens E, Vulto AG, Huys I, *et al.* Policies for biosimilar uptake in Europe: an overview. *PLOS ONE* 2017;**12**:e0190147. doi:10.1371/journal.pone.0190147

226 Bundesministerium der Justiz und für Verbraucherschutz. SGB 5 - nichtamtliches Inhaltsverzeichnis. Gesetze-Im-Internetde. https://www.gesetze-im-internet.de/sgb_5/index.html#BJNR024820988BJNE017545126 (accessed 11 Apr 2020).

227 Autoriteit Consument & Markt. Sectoronderzoek TNF-alfaremmers: concurrentie voor en na toetreding van biosimilars. Den Haag. Autoriteit Consument & Markt 2019. https://www.acm.nl/sites/default/files/documents/2019-09/sectoronderzoek-tnf-alfaremmers.pdf (accessed 11 Apr 2020).

228 Dylst P, Vulto A, Simoens S. Barriers to the uptake of biosimilars and possible solutions: a Belgian case study. *PharmacoEconomics* 2014;**32**:681–91. doi:10.1007/s40273-014-0163-9

229 Rémuzat C, Dorey J, Cristeau O, *et al.* Key drivers for market penetration of biosimilars in Europe. *J Mark Access Health Policy* 2017;**5**:1–15. doi:10.1080/20016689.2016.1272308

230 Rémuzat C, Kapuśniak A, Caban A, *et al.* Supply-side and demand-side policies for biosimilars: an overview in 10 European member states. *J Mark Access Health Policy* 2017;**5**:1307315. doi:10.1080/20016689.2017.1307315

231 Jensen TB, Bartels D, Sædder EA, *et al.* The Danish model for the quick and safe implementation of infliximab and etanercept biosimilars. *Eur J Clin Pharmacol* 2019;**76**:35–40. doi:10.1007/s00228-019-02765-3

232 Achtung teure Fehlanreize! - santésuisse - Die Schweizer Krankenversicherer. https://www.santesuisse.ch/it/details (accessed 25 Jan 2021).

233 Graudal N, Kaas-Hansen BS, Guski L, *et al.* Different original and biosimilar TNF inhibitors similarly reduce joint destruction in rheumatoid arthritis: a network meta-analysis of 36 randomized controlled trials. *Int J Mol Sci* 2019;**20**. doi:10.3390/ijms20184350

234 Kilcher G, Hummel N, Didden EM, *et al.* Rheumatoid arthritis patients treated in trial and real world settings: comparison of randomized trials with registries. *Rheumatology* 2018;**57**:354–69. doi:10.1093/rheumatology/kex394

235 Barbier L, Ebbers H, Declerck P, *et al.* The efficacy, safety and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review. *Clin Pharmacol Ther* Published Online First: 2020. doi:10.1002/cpt.1836

236 Cohen HP, Blauvelt A, Rifkin RM, *et al.* Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. *Drugs* 2018;**78**:463–78. doi:10.1007/s40265-018-0881-y

237 Feagan BG, Lam G, Ma C, *et al.* Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. *Aliment Pharmacol Ther* 2019;**49**:31–40. doi:10.1111/apt.14997

238 Strand V, Gonçalves J, Hickling TP, *et al.* Immunogenicity of Biosimilars for Rheumatic Diseases, Plaque Psoriasis, and Inflammatory Bowel Disease: A Review from Clinical Trials and Regulatory Documents. *BioDrugs Clin Immunother Biopharm Gene Ther* 2020;**34**:27–37. doi:10.1007/s40259-019-00394-x

239 Bakalos G, Zintzaras E. Drug discontinuation in studies including a switch from an originator to a biosimilar monoclonal antibody: a systematic literature review. *Clin Ther* 2019;**41**:155-173.e13. doi:10.1016/j.clinthera.2018.11.002

240 McKinnon RA, Cook M, Liauw W, *et al.* Biosimilarity and interchangeability: principles and evidence: a systematic review. *BioDrugs* 2018;**32**:27–52. doi:10.1007/s40259-017-0256-z

241 Zeidler J, Mittendorf T, Müller R, *et al.* Biologic TNF inhibiting agents for treatment of inflammatory rheumatic diseases: dosing patterns and related costs in Switzerland from a payers perspective. *Health Econ Rev* 2012;**2**:20. doi:10.1186/2191-1991-2-20

242 Hülsemann JL, Mittendorf T, Merkesdal S, *et al.* Direct costs related to rheumatoid arthritis: the patient perspective. *Ann Rheum Dis* 2005;**64**:1456–61. doi:10.1136/ard.2004.031880

243 Network Biosimilars CH. Positionspapier. Wege, um das Sparpotential durch Biosimilars voll auszuschöpfen. https://www.network-biosimilars.ch/images/nwbios/Dokumente/Positionspapier_Network_Biosimilars_CH_20200527.pdf

244 Intergenerika swiss generics and biosimilars. Positionspapier der Intergenerika zu Biosimilars. 2018.http://www.intergenerika.ch/wp-content/uploads/2018/05/Vision-und-Positionspapier-der-Intergenerika-zu-Biosimilars_final_April-2018.pdf

245 Mehr SR, Brook RA. Factors influencing the economics of biosimilars in the US. *J Med Econ* 2017;**20**:1268–71. doi:10.1080/13696998.2017.1366325

246 Aerts LA van, Smet KD, Reichmann G, *et al.* Biosimilars entering the clinic without animal studies. *mAbs* 2014;**6**:1155–62. doi:10.4161/mabs.29848

247 ANSM. État des lieux sur les médicaments biosimilaires. Saint-Denis CEDEX. Agence Nationale de Sécurité du Médicament et des Produits de Santé 2016. https://www.ansm.sante.fr/content/download/88209/1110173/version/1/file/Rapport-biosimilaires-2mai2016.pdf (accessed 21 Feb 2020).

248 Agenzia Italiana del Farmaco. Domande e risposte su farmaci biosimilari. https://aifa.gov.it/domande-e-risposte-su-farmaci-biosimilari (accessed 21 Feb 2020).

249 Agenzia Italiana del Farmaco. Secondo Position Paper AIFA sui farmaci biosimilari. Agenzia Italiana del Farmaco 2018. https://www.aifa.gov.it/sites/default/files/pp_biosimilari_27.03.2018.pdf (accessed 21 Feb 2020).

250 Al-Sabbagh A, Olech E, McClellan JE, *et al.* Development of biosimilars. *Semin Arthritis Rheum* 2016;**45**:S11–8. doi:10.1016/j.semarthrit.2016.01.002

251 Bhatt V. Current market and regulatory landscape of biosimilars. *Am J Manag Care* 2018;**24**:S451–6.

252 British Columbia Ministry of Health. Biosimilars Initiative for Prescribers - Province of British Columbia. British Columbia Ministry of Health https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/biosimilars-initiative-prescribers (accessed 21 Feb 2020).

253 Bundesamt für Sicherheit im Gesundheitswesen. Generika und Biosimilars. Bundesamt für Sicherheit im Gesundheitswesen 2019. https://www.basg.gv.at/konsumentinnen/wissenswertes-ueber-arzneimittel/arzneimittel/generika-und-biosimilars (accessed 21 Feb 2020).

254 Carver KH, Elikan J, Lietzan E. An unofficial legislative history of the Biologics Price Competition and Innovation Act of 2009. *Food Drug Law J* 2010;**65**:671.

255 Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Biosimilars and interchangeable biosimilars: licensure for fewer than all conditions of use for which the reference product has been licensed guidance for industry. Center for Drug Evaluation and Research 2020. https://www.fda.gov/media/134932/download (accessed 9 Mar 2020).

256 Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Considerations in demonstrating interchangeability with a reference product: guidance for industry. Center for Drug Evaluation and Research 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-demonstrating-interchangeability-reference-product-guidance-industry (accessed 16 Apr 2020).

257 Center for Drug Evaluation and Research. Questions and answers on biosimilar development and the BPCI Act: guidance for industry. Center for Drug Evaluation and Research 2019. https://www.fda.gov/media/119258/download (accessed 21 Feb 2020).

258 Center for Drug Evaluation and Research. Biosimilars development, review, and approval. Center for Drug Evaluation and Research 2017. https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval#process (accessed 16 Apr 2020).

259 Chance K. FDA expectations for demonstrating interchangeability. *Ther Innov Regul Sci* 2018;**52**:369–73. doi:10.1177/2168479018755702

260 Chapman K, Adjei A, Baldrick P, *et al.* Waiving in vivo studies for monoclonal antibody biosimilar development: national and global challenges. *mAbs* 2016;**8**:427–35. doi:10.1080/19420862.2016.1145331

261 Chen BK, Yang YT, Bennett CL. Why biologics and biosimilars remain so expensive: despite two wins for biosimilars, the Supreme Court's recent rulings do not solve fundamental barriers to competition. *Drugs* 2018;**78**:1777–81. doi:10.1007/s40265-018-1009-0

262 Christl LA, Woodcock J, Kozlowski S. Biosimilars: the US regulatory framework. *Annu Rev Med* 2017;**68**:243–54. doi:10.1146/annurev-med-051215-031022

263 College ter Beoordeling van Geneesmiddelen. Vragen en antwoorden biosimilar geneesmiddelen. Utrecht. College ter Beoordeling van Geneesmiddelen 2015. https://www.cbg-meb.nl/binaries/college-ter-beoordeling-van-geneesmiddelen/documenten/publicaties/2015/01/01/vragen-en-antwoorden-biosimilar-geneesmiddelen/vragenenantwoorden-biosimilargeneesmiddelen.pdf (accessed 21 Feb 2020).

264 Daller J. Biosimilars: a consideration of the regulations in the United States and European Union. *Regul Toxicol Pharmacol* 2016;**76**:199–208. doi:10.1016/j.yrtph.2015.12.013

265 Dougherty MK, Zineh I, Christl L. Perspectives on the current state of the biosimilar regulatory pathway in the United States. *Clin Pharmacol Ther* 2018;**103**:36–8. doi:10.1002/cpt.909

266 EMA. Biosimilar medicines: marketing authorisation. 2018.https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/biosimilar-medicines-marketing-authorisation (accessed 10 Apr 2020).

267 Committee for Human Medicinal Products (CHMP). Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues. London. European Medicines Agency 2012. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf (accessed 10 Apr 2020).

268 Committee for Human Medicinal Products (CHMP). Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process: non-clinical and clinical issues. London. European Medicines Agency 2007. https://www.ema.europa.eu/documents/scientific-guideline/guideline-comparability-biotechnology-derived-medicinal-products-after-change-manufacturing-process_en.pdf (accessed 21 Feb 2020).

269 Committee for Proprietary Medicinal Products. Note for guidance on biotechnological/biological products subject to changes in their manufacturing process. London. European Medicines Agency 2005. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-e-comparability-biotechnological/biological-products-step-5_en.pdf (accessed 10 Apr 2020).

270 Endrenyi L, Markus R. Interchangeability of biological drug products-FDA draft guidance. *J Biopharm Stat* 2019;**29**:1003–10. doi:10.1080/10543406.2019.1607369

271 Epstein M. Food and Drug Administration guidances on biosimilars: an update for the gastroenterologist. *Ther Adv Gastroenterol* 2018;**11**. doi:10.1177/1756284818799600

272 Falit BP, Singh SC, Brennan TA. Biosimilar competition in the United States: statutory incentives, payers, and pharmacy benefit managers. *Health Aff (Millwood)* 2015;**34**:294–301. doi:10.1377/hlthaff.2014.0482

273 FDA, FTC. Joint Statement of the Food & Drug Administration and the Federal Trade Commission regarding a collaboration to advance competition in the biologic marketplace. Food & Drug Administration and Federal Trade Commission 2020. https://www.fda.gov/media/134864/download (accessed 21 Feb 2020).

274 Feagan BG, Choquette D, Ghosh S, *et al.* The challenge of indication extrapolation for infliximab biosimilars. *Biologicals* 2014;**42**:177–83. doi:10.1016/j.biologicals.2014.05.005

275 Fimea. Interchangeability of biosimilars: position of Finnish Medicines Agency Fimea. Finnish Medicines Agency 2015. https://www.fimea.fi/documents/542809/838272/29197_Biosimilaarien_vaihtokelpoisuus_EN.pdf (accessed 21 Feb 2020).

276 Fimea. Biological medicinal products. Finnish Medicines Agency https://www.fimea.fi/web/en/pharmaceutical_safety_and_information/biological-medicinal-products (accessed 21 Feb 2020).

277 Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die Einleitung eines Stellungnahmeverfahrens zur Änderung der Arzneimittel-Richtlinie (AM-RL): § 40a (neu) – Austausch von biotechnologisch hergestellten biologischen Arzneimitteln. Berlin. Gemeinsamer Bundesausschuss 2020. https://www.g-ba.de/bewertungsverfahren/beratungsthemen/4164/ (accessed 21 Feb 2020).

278 Gitter DM. Informed by the European Union experience: what the United States can anticipate and learn from the European Union's regulatory approach to biosimilars. *Seton Hall Law Rev* 2011;**41**:559–92.

279 Ha CY, Kornbluth A. A critical review of biosimilars in IBD: the confluence of biologic drug development, regulatory requirements, clinical outcomes, and big business. *Inflamm Bowel Dis* 2016;**22**:2513–26. doi:10.1097/MIB.0000000000000886

280 Health Canada. Guidance document: information and submission requirements for biosimilar biologic drugs. Ottawa, ON. Health Canada 2016. https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs-1.html (accessed 21 Feb 2020).

281 Heinemann L, Khatami H, McKinnon R, *et al.* An overview of current regulatory requirements for approval of biosimilar insulins. *Diabetes Technol Ther* 2015;**17**:510–26. doi:10.1089/dia.2014.0362

282 Heled Y. The case for disclosure of biologics manufacturing information. *J Law Med Ethics* 2019;**47**:54–78. doi:10.1177/1073110519898043

283 Hung A, Vu Q, Mostovoy L. A systematic review of U.S. biosimilar approvals: what evidence does the FDA require and how are manufacturers responding? *J Manag Care Spec Pharm* 2017;**23**:1234–44. doi:10.18553/jmcp.2017.23.12.1234

284 Juillard-Condat B, Taboulet F. Chapitre 5. L'encadrement des médicaments biosimilaires à la croisée des logiques sanitaires et économiques. *J Int Bioéthique Déthique Sci* 2018;**29**:87–111. doi:10.3917/jibes.292.0087.

285 Kay J. Biosimilars: a regulatory perspective from America. *Arthritis Res Ther* 2011;**13**:112. doi:10.1186/ar3310

286 Kirchhoff CF, Wang X-ZM, Conlon HD, *et al.* Biosimilars: key regulatory considerations and similarity assessment tools. *Biotechnol Bioeng* 2017;**114**:2696–705. doi:10.1002/bit.26438

287 Lemery SJ, Ricci MS, Keegan P, *et al.* FDA's approach to regulating biosimilars. *Clin Cancer Res* 2017;**23**:1882–5. doi:10.1158/1078-0432.CCR-16-1354

288 Li E, Lobaina E. Application of the FDA biosimilar extrapolation framework to make off-label determinations. *J Manag Care Spec Pharm* 2017;**23**:1227–32. doi:10.18553/jmcp.2017.23.12.1227

289 Lucio S. The complexities of biosimilars and the regulatory approval process. *Am J Manag Care* 2018;**24**:S231–6.

290 Ministerio de sanidad, consumo y bienestar social. Plan de acción para fomentar la utilización de los medicamentos reguladores del mercadoen el sistema nacional de salud: medicamentos biosimilares y medicamentos genéricos. Madrid. Ministerio de sanidad, consumo y bienestar social 2019. https://www.mscbs.gob.es/profesionales/farmacia/pdf/PlanAccionSNSmedicamentosReguladoresMercado.pdf (accessed 21 Feb 2020).

291 NHS England. Commissioning framework for biological medicines (including biosimilar medicines). NHS England 2017. https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf (accessed 21 Feb 2020).

292 NHS England. Biosimilar medicines. https://www.england.nhs.uk/medicines/biosimilar-medicines/ (accessed 21 Feb 2020).

293 Nikolov NP, Shapiro MA. An FDA perspective on the assessment of proposed biosimilar therapeutic proteins in rheumatology. *Nat Rev Rheumatol* 2017;**13**:123–8. doi:10.1038/nrrheum.2016.204

294 O'Callaghan J, Barry SP, Bermingham M, *et al.* Regulation of biosimilar medicines and current perspectives on interchangeability and policy. *Eur J Clin Pharmacol* 2019;**75**:1–11. doi:10.1007/s00228-018-2542-1

295 Olech E. Biosimilars: rationale and current regulatory landscape. *Semin Arthritis Rheum* 2016;**45**:S1-10. doi:10.1016/j.semarthrit.2016.01.001

296 Paradise J. The legal and regulatory status of biosimilars: how product naming and state substitution laws may impact the United States healthcare system. *Am J Law Med* 2015;**41**:49–84. doi:10.1177/0098858815591509

297 Paul-Ehrlich-Institut. Po-si-ti-on des Paul-Ehr-lich-In-sti-tuts zum Ein-satz von Bio-si-mi-lars. Paul-Ehrlich-Institut 2019. https://www.pei.de/DE/arzneimittel/antikoerper/monoklonale-antikoerper/monoklonale-antikoerper-node.html?cms_tabcounter=1 (accessed 21 Feb 2020).

298 Rahalkar H, Cetintas HC, Salek S. Quality, non-clinical and clinical considerations for biosimilar monoclonal antibody development: EU, WHO, USA, Canada, and BRICS-TM regulatory guidelines. *Front Pharmacol* 2018;**9**:1079. doi:10.3389/fphar.2018.01079

299 Rathore AS, Bhargava A. Biosimilars in developed economies: overview, status, and regulatory considerations. *Regul Toxicol Pharmacol* 2020;**110**:104525. doi:10.1016/j.yrtph.2019.104525

300 Renwick MJ, Smolina K, Gladstone EJ, *et al.* Postmarket policy considerations for biosimilar oncology drugs. *Lancet Oncol* 2016;**17**:e31-38. doi:10.1016/S1470-2045(15)00381-2

301 Scott BJ, Klein AV, Wang J. Biosimilar monoclonal antibodies: a Canadian regulatory perspective on the assessment of clinically relevant differences and indication extrapolation. *J Clin Pharmacol* 2015;**55 Suppl 3**:S123-132. doi:10.1002/jcph.339

302 Sowinski-Raff L. Approval process: an overview of biosimilars in the oncology setting. *Clin J Oncol Nurs* 2018;**22**:13–8. doi:10.1188/18.CJON.S1.13-18

303 Statens legemiddelverk. Switching between a reference product and a biosimilar - Legemiddelverket. 2017. https://legemiddelverket.no/nyheter/switching-between-a-reference-product-and-a-biosimilar (accessed 21 Feb 2020).

304 Stevenson JG. Clinical data and regulatory issues of biosimilar products. *Am J Manag Care* 2015;**21**:s320-330.

305 Swartenbroekx N, Farfan-Portet, Espín J, *et al.* Incentives for market penetration of biosimilars in Belgium and in five European countries. *J Pharm Belg* 2014;:36–46.

306 Swissmedic. Wegleitung Zulassung Humanarzneimittel nach Art. 13 HMG HMV4. Bern. Swissmedic 2020. https://www.swissmedic.ch/dam/swissmedic/de/dokumente/zulassung/zl_hmv_iv/zl000_00_019d_vvanleitungzulassungimauslandbereitszugelassenerhu.pdf.download.pdf/ZL000_00_019d_WL%20Zulassung%20Humanarzneimittel%20nach%20Art.%2013%20HMG%20.pdf (accessed 21 Feb 2020).

307 Swissmedic. Wegleitung Zulassung Biosimilar HMV4. Bern. Swissmedic 2020. https://www.swissmedic.ch/dam/swissmedic/de/dokumente/zulassung/zl_hmv_iv/zl101_00_012d_wlverwaltungsverordnunganleitungzulassungaehnliche.pdf.download.pdf/ZL101_00_012d_WL%20Zulassung%20Biosimilar.pdf (accessed 21 Feb 2020).

308 Australian Government Department of Health Therapeutic Goods Administration. Biosimilar medicines regulation. Australian Government Department of Health Therapeutic Goods Administration 2018. https://www.tga.gov.au/sites/default/files/biosimilar-medicines-regulation.pdf (accessed 21 Feb 2020).

309 Tsiftsoglou AS, Ruiz S, Schneider CK. Development and regulation of biosimilars: current status and future challenges. *BioDrugs* 2013;**27**:203–11. doi:10.1007/s40259-013-0020-y

310 Tu C-L, Wang Y-L, Hu T-M, *et al.* Analysis of pharmacokinetic and pharmacodynamic parameters in EU- versus US-licensed reference biological products: are in vivo bridging studies justified for biosimilar development? *BioDrugs* 2019;**33**:437–46. doi:10.1007/s40259-019-00357-2

311 Wang J, Chow S-C. On the regulatory approval pathway of biosimilar products. *Pharmaceuticals* 2012;**5**:353–68. doi:10.3390/ph5040353

312 Webster CJ, Woollett GR. A ‘global reference’ comparator for biosimilar development. *BioDrugs* 2017;**31**:279–86. doi:10.1007/s40259-017-0227-4

313 WHO. Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2, technical report series No. 977, 2009. Geneva. World Health Organization 2009. https://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf (accessed 9 Mar 2020).

314 Wong AY-T, Rumore MM, Chan AW-K. Biosimilars in the United States: emerging issues in litigation. *BioDrugs* 2017;**31**:189–205. doi:10.1007/s40259-017-0216-7

13 Appendices

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

Appendix table 1 Search strategy for the Cochrane Library

Initial search for scoping report:

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

As Cochrane made some changes to their algorithm between the initial search for the scoping report and the search update for the HTA report, we only considered the studies published in 2020 from the search update:

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	20,846
#2	Intervention and health	(infliximab OR remicade OR cost* OR economic* OR budget* OR "pharmaco-economic*" OR expenditure* OR pric* OR priz* OR financ*	240,820

Step	Item	Search string	Hits
	economics	OR value* OR mone* OR markov* OR "monte carlo" OR "decision tree*" OR “microsimulation” OR “discrete event simulation”):ti,ab,kw	
#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	246,747
#4	Combine	#1 AND #2 AND #3	1,021
#5	Publication year 2020, trials	#1 AND #2 AND #3 with Publication Year from 2020 to 2020, in Trials	25
#6	Publication year 2020, reviews	#1 AND #2 AND #3 with Cochrane Library publication date Between Jan 2020 and Dec 2020, in Cochrane Reviews	3
#7	Combine	#5 AND #6	28

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*)	187,608
#2	Intervention and health economics	((MH "Infliximab") OR (MH "Economics+")) OR TI (infliximab OR remicade OR cost* OR economic* OR budget* OR "pharmacoeconomic*" 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*")	3,235,749
#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 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*)))	4,818
#4	Combine	#1 AND #2 AND #3	339

Step	Item	Search string	Hits
#5	Exclude non-human studies	#1 AND #2 AND #3 NOT ((MH "Animals") NOT (MH "Humans"))	337

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	332,210
#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	4,041,674
#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)	8,937
#4	Combine	#1 AND #2 AND #3	1,149
#5	Exclude non-human studies	#1 AND #2 AND #3 NOT ([animals]/lim NOT [humans]/lim)	1,137

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*	62
#2	Intervention and health economics	TX infliximab OR remicade OR cost* OR economic* OR budget* OR "pharmacoeconomic*" 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”	1,487,341

Step	Item	Search string	Hits
#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*))	45
#4	Combine	#1 AND (#2 OR #3)	53

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*)	6,432
#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”)	700,902
#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*))	115
#4	Combine	#1 AND #2 AND #3	0

13.2 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/)

13.3 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)

13.4 Studies excluded during full text review

13.4.1 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 Baker JF, Leonard CE, Lo Re V 3rd, *et al.* Biosimilar Uptake in Academic and Veterans Health Administration Settings: Influence of Institutional Incentives. Arthritis & rheumatology (Hoboken, NJ) 2020;72:1067–71. 10.1002/art.41277 *not target population*

6 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*

7 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 and/or intervention*

8 Barker J, Girolomoni G, Egeberg A, *et al.* Anti-TNF biosimilars in psoriasis: from scientific evidence to real-world experience. The Journal of dermatological treatment 2020;31:794–800. 10.1080/09546634.2019.1610553 *not target publication status*

9 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*

10 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*

11 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*

12 Bodio C, Grossi C, Pregnolato F, *et al.* Personalized medicine in rheumatoid arthritis: How immunogenicity impacts use of TNF inhibitors. Autoimmunity reviews 2020;19:102509. 10.1016/j.autrev.2020.102509 *not target comparator and/or intervention*

13 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*

14 Borras J, Gracia-Pérez A, Valcuende Rosique A, *et al.* Clinical and economic impact of infliximab biosimilar inflectra in rheumatoid arthritis, psoriatic arthropathy and ankylosing spondylitis naÏve and switched patients: 5 years of follow-up. European Journal of Hospital Pharmacy 2020;27:A99. 10.1136/ejhpharm-2020-eahpconf.212 *not target publication status*

15 Braun J, Baraliakos X, Kudrin A, *et al.* Striking Discrepancy in the Development of Anti-Drug Antibodies (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*

16 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*

17 Bufan B, Jančić I, Stojić-Vukanić Z. Inhibitors of tumor necrosis factor-α and mechanisms of their action. Arhiv za Farmaciju 2020;70:109–29. 10.5937/arhfarm2003109B *not target publication status*

18 Cantini F, Niccoli L, Franchi G, *et al.* The nocebo effect in rheumatology: An unexplored issue. Israel Medical Association Journal 2020;22:185–90. *not target publication status*

19 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*

20 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*

21 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*

22 Claytor JD, Redberg RF. Product Hopping - An Expensive and Wasteful Practice. JAMA Internal Medicine 2020;180:1154–5. 10.1001/jamainternmed.2020.2736 *not target publication status*

23 Codreanu C, Sirova K, Jarosova, K, *et al.* Effectiveness and Safety of CT- P13 (Biosimilar Reference Infliximab) in a Real-Life Setting in 151 Patients with Rheumatoid Arthritis and Ankylosing Spondylitis: A Mid-Term Interim Analysis. American College of Rheumatology Meeting Abstracts 2016. *not target publication status*

24 Cohen S, Alten R, Kameda H, *et al.* A randomized controlled trial comparing PF-06438179/GP1111 (an infliximab biosimilar) and infliximab reference product for treatment of moderate to severe active rheumatoid arthritis despite methotrexate therapy. Arthritis Research & Therapy. Published Online First: 2018.https://arthritis-research.biomedcentral.com/articles/10.1186/s13075-018-1646-4. *duplicate*

25 Cohen JD, Tropé S, Paubel P, *et al.* Preconceived notions about biosimilars—a French experience. Clinical Rheumatology 2020;39:2251–4. 10.1007/s10067-020-05229-7 *not target publication status*

26 Cohen SB, Radominski SC, Kameda H, *et al.* Long-term Efficacy, Safety, and Immunogenicity of the Infliximab (IFX) Biosimilar, PF-06438179/GP1111, in Patients with Rheumatoid Arthritis After Switching from Reference IFX or Continuing Biosimilar Therapy: Week 54-78 Data From a Randomized, Double-Blind, Phase III Trial. Biodrugs: Clinical Immunotherapeutics, Biopharmaceuticals And Gene Therapy Published Online First: 14 January 2020. 10.1007/s40259-019-00403-z *not target comparator and/or intervention*

27 *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*

28 Convertino I, Lucenteforte E, Gini R, *et al.* Utilisation patterns and clinical impact of the introduction of infliximab-biosimilar in Tuscany, Italy: real world evidence following the recommendation of switching for non-medical reasons. Clinical and experimental rheumatology Published Online First: 2020.http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=32828145&site=ehost-live *fulltext not available*

29 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 comparator and/or intervention*

30 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*

31 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*

32 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*

33 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*

34 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*

35 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*

36 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*

37 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*

38 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*

39 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*

40 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*

41 Gasteiger C, Jones ASK, Kleinstäuber M, *et al.* Effects of Message Framing on Patients' Perceptions and Willingness to Change to a Biosimilar in a Hypothetical Drug Switch. Arthritis Care and Research 2020;72:1323–30. 10.1002/acr.24012 *not target comparator and/or intervention*

42 Gasteiger C, Lobo M, Dalbeth N, *et al.* Patients' beliefs and behaviours are associated with perceptions of safety and concerns in a hypothetical biosimilar switch. Rheumatology international Published Online First: 2020. 10.1007/s00296-020-04576-7 *not target comparator and/or intervention*

43 Gavrila BI, Ciofu C, MacOvei L, *et al.* A breakthrough diagnostic protein, 14-3-3 ETA, can help us identify patients who will respond to infliximab and its biosimilar in rheumatoid arthitis? J Clin Rheumatol 2019;25:S3. 10.1097/RHU.0000000000001070 *not target publication status*

44 Genovese MC, Sanchez-Burson J, Oh M, *et al.* Clinical similarity of ABP 710 with infliximab (reference product) in subjects with moderate to severe rheumatoid arthritis. Ann Rheum Dis 2019;78:1648–9. 10.1136/annrheumdis-2019-eular.4928 *not target publication status*

45 Ghosh S, Ghosh A. Recent advances in rheumatology. Journal of the Indian Medical Association 2020;118:25–8. *not target publication status*

46 Gibofsky A, Garg V, Yang M, *et al.* Estimating the short-term costs associated with non-medical switching in rheumatic diseases. Ann Rheum Dis 2018;77:1372. 10.1136/annrheumdis-2018-eular.7463 *not target publication status*

47 Gibofsky A, Skup M, Yang M, *et al.* Real-world outcomes in stable originator biologic-treated adult patients who stayed on the therapy versus those who switched to biosimilar: A retrospective chart review study in Europe. Ann Rheum Dis 2019;78:1582. 10.1136/annrheumdis-2019-eular.4303 *not target publication status*

48 Glintborg B, Sørensen I, Loft A. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry Ann Rheum Dis 2017. *duplicate*

49 Goll GL, Bolstad N, Iria I, *et al.* The fine specificity of anti-drug antibody responses to originator and biosimilar infliximab: Analyses across five diseases from the 52-week randomized nor-switch study. Ann Rheum Dis 2018;77:852–3. 10.1136/annrheumdis-2018-eular.5554 *not target publication status*

50 Goll GL, Bolstad N, Iria I, *et al.* Immunogenicity of originator and biosimilar infliximab: Anti-drug antibody occurence, cross-reactivity and epitope specificities across six diseases. Analyses from a norwegian randomized switching trial. Arthritis Rheum 2018;70:771–2. 10.1002/art.40700 *not target publication status*

51 Goll GL, Jørgensen KK, Sexton J, *et al.* Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial. Journal Of Internal Medicine 2019;285:653–69. 10.1111/joim.12880 *not target comparator and/or intervention*

52 Goll GL, Kvien TK. An Opportunity Missed: Biosimilars in the United States. Arthritis and Rheumatology 2020;72:1046–8. 10.1002/art.41280 *not target publication status*

53 González Fernández M, Villamañán E, Jiménez-Nácher I, *et al.* Cost evolution of biological drugs in rheumatoid arthritis patients in a tertiary hospital: Influential factors on price. Reumatol Clin Published Online First: 2019. 10.1016/j.reuma.2019.10.004 *not target comparator and/or intervention*

54 González-Fernández MÁ, Bueno EV, Jiménez-Nácher I, *et al.* Sat0565 Cost Evolution of Biological Agents for the Treatment of Rheumatoid Arthritis in a Tertiary Hospital Influential Factors in Price. Annals of the Rheumatic Diseases 2019;78:1375–1375. 10.1136/annrheumdis-2019-eular.1900 *not target publication status*

55 Gudu T, Bojinca V, Peltea A, *et al.* Biologic therapy switch-ranking of the patients values. Ann Rheum Dis 2014;73. 10.1136/annrheumdis-2014-eular.5114 *not target publication status*

56 Gutermann L, Apparuit M, Boissinot L, *et al.* Evaluation of infliximab (remicade) substitution by infliximab biosimilar (inflectra): Cost savings and therapeutic maintenance. Euro J Hosp Pharm Sci Pra 2017;24:A67–8. 10.1136/ejhpharm-2017-000640.149 *not target publication status*

57 HAS. Évaluation médico-économique des traitements de fond biologiques dans la prise en charge de la polyarthrite rhumatoïde. Saint-Denis La Plaine: : Haute Autorité de Santé 2019. [cited 2020 11 March] https://has-

sante.fr/jcms/c_2580906/fr/evaluation-medico-economique-des-traitements-de-fond-biologiques-dans-la-prise-en-charge-de-la-polyarthrite-rhumatoide. *not target comparator and/or intervention*

58 Iannazzo S, Benucci M, Favalli EG. Tocilizumab after a first-line with anti-tnf in rheumatoid arthritis: A cost-consequence analysis in the Italian setting. Value Health 2017;20:A533. 10.1016/j.jval.2017.08.762 *not target comparator and/or intervention* 59 Iannazzo S, Furneri G, Demma F, *et al.* The Burden of Rheumatic Diseases: An Analysis of an Italian Administrative Database. Rheumatol Ther 2016;3:167–77. 10.1007/s40744-016-0034-2 *not target publication status*

60 Jha A, Upton A, Dunlop W. Budget impact analysis of introducing biosimilar infliximab for the treatment of auto immune disorders in five European countries. Value in Health 2014;17:A525. 10.1016/j.jval.2014.08.1655 *not target publication status*

61 Jones AR, Batty A, Lloyd LA, *et al.* Using NHS resources wisely: A snapshot of biologic and small molecule agent prescribing at the peter maddison rheumatology centre. Rheumatology (United Kingdom) 2020;59:ii24–5. 10.1093/rheumatology/keaa111.013 *not target publication status*

62 Jørgensen TS, Skougaard M, Asmussen HC, *et al.* Communication strategies are highly important to avoid nocebo effect when performing non-medical switch from originator product to biosimilar product: Danish results from applying the Parker model a qualitative 3-step research model. Arthritis Rheum 2017;69.http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L618912873. *not target publication status*

63 Jørgensen K.K., Olsen I.C., Goll G.L., *et al.* Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 2017;389:2304–16. 10.1016/S0140-6736(17)30068-5 *not relevant outcome*

64 JPRN-UMIN000021492. To investigate the safety of switch from infliximab biosimilar 1 in rheumatoid arthritis patients. http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000021492 Published Online First: 2016.https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01843886/full. *not target publication status*

65 Juday T, Skup M, Streuper C, *et al.* Impact of non-medical switching of anti-tumor necrosis factor agents on healthcare costs in Europe. United Eur Gastroenterol J 2016;4:A259–60. 10.1177/2050640616663689 *not target publication status*

66 Kameda H, Uechi E, Atsumi T, *et al.* A comparative study of PF-06438179/GP1111 (an infliximab biosimilar) and reference infliximab in patients with moderate to severe active rheumatoid arthritis: A subgroup analysis. International journal of rheumatic diseases 2020;23:876–81. 10.1111/1756-185X.13846 *not relevant outcome*

67 Kanters TA, Stevanovic J, Huys I, *et al.* Adoption of biosimilar infliximab for rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel diseases in the EU5: a budget impact analysis using a Delphi panel. Frontiers In Pharmacology 2017;8:322–322. 10.3389/fphar.2017.00322 *duplicate*

68 Kim J, Hong J, Kudrin A. year budget impact analysis of biosimilar infliximab for the treatment of rheumatoid arthritis in UK, Italy, France and Germany. Arthritis Rheumatol Published Online First:

2014.http://www.medisquare.be/wp-content/uploads/2016/03/acrabstracts_org_abstract_5_year_budget_impact_analysis_of_b.pdf. *not target publication status*

69 Kim H-A, Lee E, Lee S-K, *et al.* Retention Rate and Safety of Biosimilar CT-P13 in Rheumatoid Arthritis: Data from the Korean College of Rheumatology Biologics Registry. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy 2020;34:89–98. 10.1007/s40259-019-00393-y *not target setting*

70 Klink A, Sadik K, Lee C, *et al.* Real-world treatment patterns of rheumatoid arthritis patients who switched from infliximab to iinfliximab-dyyb. J Manag Care Spec Pharm 2019;25:S81–2. *not target publication status*

71 Langfelder R, Cattaneo S, Migliavada L, *et al.* The biosimilar infliximab in rheumatoid arthritis: Use and potential savings in asl milano. Euro J Hosp Pharm 2016;23:A60–1. 10.1136/ejhpharm-2016-000875.138 *not target publication status*

72 Lechat P. [Biosimilar medicines: Regulatory issues and medico-economic impacts]. Bulletin de l'Academie nationale de medecine 2020;204:877–83. 10.1016/j.banm.2020.07.050 *not target publication status*

73 Lekander I. The cost-effectiveness of tnf-inhibitors for the treatment of rheumatoid arthritis in Swedish clinical practice. European Journal of Health Economics 2013;14:863–73. *not target comparator and/or intervention*

74 Lila A.M., Mazurov V.I., Denisov L.N., *et al.* A phase III study of BCD-055 compared with innovator infliximab in patients with active rheumatoid arthritis: 54-week results from the LIRA study. Rheumatol Int 2019;39:1537–46. 10.1007/s00296-019-04359-9 *biosimilar not approved in either Switzerland, EU or USA*

75 Linares A, Fernandez Cuerva C, Asensi Diez R, *et al.* Budgetary impact of biosimilar prescription in the treatment of rheumatic diseases. European Journal of Hospital Pharmacy 2020;27:A133. 10.1136/ejhpharm-2020-eahp-conf.282 *not target publication status*

76 Lopez Suarez JM, Lopez Chozas JM, Rubio Romero E. Safety of biosimilar infliximab use in a medical day hospital: A case-series. Ann Rheum Dis 2017;76:574–5. 10.1136/annrheumdis-2017-eular.6470 *not target publication status*

77 Lorenzoni V, Trieste L, Mosca M, *et al.* The economic impact of the introduction of infliximab-biosimilar: Preliminary results from a study on rheumatologic patients in Tuscany, Italy. Pharmacoepidemiol Drug Saf 2019;28:9. 10.1002/pds.4864 *not target publication status*

78 Mahon R, Cassel T, Balkin PE, *et al.* Estimating the appropriate price discounts for biosimilars in the treatment of rheumatoid arthritis in the nordic setting using an excel-based interactive tool. Value Health 2016;19:A378. *not target publication status*

79 Malpas A, Steel L, Mills K, *et al.* Switching from remicade to biosimilar infliximab: An evaluation of efficacy, safety and patient satisfaction. Rheumatology 2017;56:ii69. 10.1093/rheumatology/kex062 *not target publication status*

80 Manova M, Savova A, Vasileva M, *et al.* Comparative price analysis of biological products for treatment of rheumatoid arthritis. Front Pharmacol 2018;9. 10.3389/fphar.2018.01070 *not target study design*

81 Matcham F, Davies R, Hotopf M, *et al.* The relationship between depression and biologic treatment response in rheumatoid arthritis: an analysis of the British Society for Rheumatology Biologics Register. Rheumatology 2018;57:835–43. 10.1093/rheumatology/kex528 *not target comparator and/or intervention*,

82 Matsuno H., Matsubara T. A randomized double-blind parallel-group phase III study to compare the efficacy and safety of NI-071 and infliximab reference product in Japanese patients with active rheumatoid arthritis refractory to methotrexate. Mod Rheumatol 2019;29:919–27. 10.1080/14397595.2018.1533063 *biosimilar not approved in either Switzerland, EU or US*

83 Moorthy A, Hall K, Walton S. Biosimilars switch in a multi-ethnic rheumatology patient group. Rheumatology 2019;58:iii83–4. 10.1093/rheumatology/kez108.008 *not target publication status*

84 Moulenat T, Fargier E, Fayard C, *et al.* Economic impact of infliximab biosimilar referencing in the hospital. Euro J Hosp Pharm Sci Pra 2019;26:A21–2. 10.1136/ejhpharm-2019-eahpconf.46 *not target publication status*

85 NCT01936181. A Study Comparing SB2 to Remicade® in Subjects With Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy. https://clinicaltrials.gov/show/NCT01936181 Published Online First: 2013.https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02037504/full. *not target publication status*

86 NCT02683564. BOW015 (Infliximab-EPIRUS) and Infliximab in Patients With Active Rheumatoid Arthritis: the UNIFORM Study. https://clinicaltrials.gov/show/NCT02683564 Published Online First: 2016.https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01555838/full. *not target publication status*

87 NCT02990806. A Phase 3 Study of NI-071 in Patients With Rheumatoid Arthritis (RADIANCE). https://clinicaltrials.gov/show/NCT02990806 Published Online First: 2016.https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01560580/full. *not target publication status*

88 Sint Maartenskliniek Nijmegen, Maartenskliniek Woerden, Radboud University Medical Center Nijmegen, Rijnstate Ziekenhuis. The effect of switching treatment from innovator infliximab to infliximab biosimilar on efficacy, safety and immunogenicity in patients with rheumatoid arthritis, spondyloarthritis or psoriatic arthritis in daily clinical care [Nederlands Trial Register no. NTR5279]. Amsterdam: Dutch Cochrane Centre; 2015. *not target publication status*

89 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*

90 Palaparthy R, Rehman MI, von Richter O, *et al.* Population pharmacokinetics of PF-06438179/GP1111 (an infliximab biosimilar) and reference infliximab in patients with moderately to severely active rheumatoid arthritis. Expert Opin Biol Ther 2019;19:1065–74. 10.1080/14712598.2019.1635583 *not target study design*

91 Palaparthy R, Schmitt S, Rehman MI, *et al.* Incidence and impact of immunogenicity in a randomised, double-blind phase III study comparing a proposed infliximab biosimilar (PF-06438179/GP1111) with reference infliximab. J Crohn's Colitis 2018;12:S386. *not target publication status*

92 Park W, Yoo D, Hrycaj P, *et al.* The rate of positive conversion in the quantiferon-TB gold test over 2 years among patients treated with CT-p13 or innovator infliximab in the extension studies of planetas and planetra. Ann Rheum Dis 2014;73. 10.1136/annrheumdis-2014-eular.3492 *not target publication status*

93 Patel D, Shelbaya A, Cheung R, *et al.* Cost-effectiveness of early treatment with originator biologics or their biosimilars after methotrexate failure in patients with established rheumatoid arthritis. Adv Ther 2019;36:2086–95. 10.1007/s12325-019-00986-7 *not target comparator and/or intervention*

94 Patel A, Heslin M, Scott DL, *et al.* Cost-Effectiveness of Combination Disease-Modifying Antirheumatic Drugs Versus Tumor Necrosis Factor Inhibitors in Active Rheumatoid Arthritis: a Pragmatic, Randomized, Multicenter Trial. Arthritis care & research 2020;72:334-342. 10.1002/acr.23830 *not target comparator and/or intervention*

95 Perks B. Randomized non-inferiority trial fails to find inferiority switching from infliximab originator to CT-P13 biosimilar. GaBI J 2017;6.http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L620195582. *not target publication status*

96 Piercy J, Waller J, Sullivan E, *et al.* Patient attitudes towards being prescribed biosimilars in inflammatory autoimmune diseases in Germany. Arthritis Rheum 2016;68:1788–9. 10.1002/art.39977 *not target publication status*

97 Presberg Y, Foltz V, L'Amour C, *et al.* Interchangeability from infliximab originator to infliximab biosimilar: Efficacy and safety in a prospective observational study on 89 patients. Ann Rheum Dis 2017;76:450. 10.1136/annrheumdis-2017-eular.6586 *not target publication status*

98 Prieto-Peña D, Dasgupta B. Biologic agents and small-molecule inhibitors in systemic autoimmune conditions: an update. Polish archives of internal medicine Published Online First: 2020. 10.20452/pamw.15438 *not target publication status*

99 Radtchenko J, Smith Y., Kish J., *et al.* Real-world utilization of biosimilars for management of rheumatoid arthritis (RA) in the US. Arthritis Rheum 2017;69.http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L618912382. *not target publication status*

100 Ramos Rodríguez J. Safety and effectiveness of switching to infliximab biosimilar in digestive and rheumatological pathology. Euro J Hosp Pharm Sci Pra 2018;25:A203–4. 10.1136/ejhpharm-2018-eahpconf.438 *not target publication status*

101 Reinisch W, Jahnsen J, Schreiber S, *et al.* Evaluation of the cross-reactivity of antidrug antibodies to CT-13 and infliximab reference product (Remicade): an analysis using immunoassays tagged with both agents. BioDrugs 2017;31:223–37. 10.1007/s40259-017-0219-4 *not target outcome*

102 Retamero A, Grados D., Cucurell M., *et al.* Switching biologic treatments: Experience of a regional hospital. Euro J Hosp Pharm Sci Pra 2019;26:A236–7. 10.1136/ejhpharm-2019-eahpconf.509 *not target publication status*

103 Rifbjerg-Madsen S, Christensen AW, Boesen M, *et al.* The course of pain hypersensitivity according to painDETECT in patients with rheumatoid arthritis initiating treatment: results from the prospective FRAME-cohort study. Arthritis Research & Therapy 2018;20:105–105. 10.1186/s13075-018-1581-4 *not target comparator and/or intervention*

104 Ringer A, Bellenie H., Parkes M., *et al.* Switching from originators to biosimilars using DAS28 and ultrasound to measure disease activity: Experience from Portsmouth, UK. Int J Rheum Dis 2018;21:178. 10.1111/1756-185X.13361 *not target publication status*

105 Rubio E, Ruiz A., López J., *et al.* Prospective study of 78 patients treated with infliximab biosimilar remsima®. Ann Rheum Dis 2016;75:1006. 10.1136/annrheumdis-2016-eular.5688 *not target publication status*

106 Ruiz-Argüello MB, Maguregui A, Ruiz Del Agua A, *et al.* Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. Ann Rheum Dis 2016;75:1693–6. 10.1136/annrheumdis-2015-208684 *not target outcome*

107 Scherlinger M, Schaeverbeke T, Truchetet M-E. Serum sickness-like disease after switching to biosimilar infliximab. Rheumatology 2017;56:2032–4. 10.1093/rheumatology/kex268 *no primary data*

108 Sekhon S, Rai R, Lau A, *et al.* Survey of patient perspectives on the introduction of subsequent entry biologics in Canada. J Rheumatol 2015;42:1336–7. 10.3899/jrheum.150322 *not target publication status*

109 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*

110 Shimizu T, Kawashiri S-Y, Sato S, *et al.* Discontinuation of biosimilar infliximab in Japanese patients with rheumatoid arthritis achieving sustained clinical remission or low disease activity during the IFX-SIRIUS STUDY I (the IFX-SIRIUS STUDY II): Study protocol for an interventional, multicenter, open-label, single-arm clinical trial with clinical, ultrasound and biomarker assessments. Medicine 2020;99:e21480. 10.1097/MD.0000000000021480 *not target publication status*

111 Smolen JS, Choe J.-Y., Keystone E.C., *et al.* Radiographic progression by disease activity states in patients with rheumatoid arthritis treated with SB2 or reference infliximab. Arthritis Rheum 2017;69.http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L618915936. *not target study design*

112 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*

113 Sung Y-K, Cho S.-K., Kim D., *et al.* Characteristics and outcomes of rheumatoid arthritis patients who started biosimilar infliximab. Rheumatol Int 2017;37:1007–14. 10.1007/s00296-017-3663-z *not target setting*

114 Tanaka Y., Yamanaka H., Takeuchi T., *et al.* Safety and efficacy of CT-P13 in Japanese patients with rheumatoid arthritis in an extension phase or after switching from infliximab. Mod Rheumatol 2017;27:237–45. 10.1080/14397595.2016.1206244 *not target comparator and/or intervention*

115 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 comparator and/or intervention*

116 Tweehuysen L, Van Den Bemt BJF, Van Ingen IL, *et al.* Clinical and immunogenicity outcomes after switching treatment from innovator infliximab to biosimilar infliximab in rheumatic diseases in daily clinical practice. Arthritis Rheum 2016;68:821–3. 10.1002/art.39977 *not target publication status*

117 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*

118 Van Den Hoogen FHJ, Tweehuysen L. Introduction of biosimilars in a rheumatological practice: First findings. Ned Tijdschr Dermatol Venereol 2016;26:135–6. *full text not available*

119 van Overbeeke E, De Beleyr B, de Hoon J, *et al.* Perception of originator biologics and biosimilars: a survey among Belgian rheumatoid arthritis patients and rheumatologists. BioDrugs 2017;31:447–59. 10.1007/s40259-017-0244-3 *not target comparator and/or intervention*

120 Vanderpoel J, Tkacz J, Brady BL, *et al.* Health care resource utilization and costs associated with switching biologics in rheumatoid arthritis. Clinical Therapeutics 2019;41:1080-1089.e5. 10.1016/j.clinthera.2019.04.032 *not target comparator and/or intervention* 121 Vinuesa Hernando JM, Gracia Piquer R, Fresquet Molina R, *et al.* Intravenous biosimilar prescribing trends in a third level Spanish hospital. European Journal of Hospital Pharmacy 2020;27:A121–2. 10.1136/ejhpharm-2020-eahpconf.258 *not target publication status*

122 Waller J, Sullivan E, Piercy J, *et al.* Assessing physician and patient acceptance of infliximab biosimilars in rheumatoid arthritis, ankylosing spondyloarthritis and psoriatic arthritis across Germany. Patient Prefer Adherence 2017;11:519–30. 10.2147/PPA.S129333 *not target outcome*

123 Whitehouse J, Walsh K, Papandrikopoulou A, *et al.* The cost saving potential of utilizing biosimilar medicines in biologic naive severe rheumatoid arthritis patients. Value Health 2013;16:A573. 10.1016/j.jval.2013.08.1547 *not target publication status*

124 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*

125 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*

126 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*

127 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*

128 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*

129 Yoo D.H., Prodanovic N., Jaworski J., *et al.* Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: Comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis 2017;76:355–63. 10.1136/annrheumdis-2015-208786 *not target comparator and/or intervention*

13.4.2 Studies excluded from searches for evidence on ELSO outcome searches

1 Ahmed I, Kaspar B, Sharma U. Biosimilars: impact of biologic product life cycle and European experience on the regulatory trajectory in the United States. Clin Ther 2012;34:400–19. 10.1016/j.clinthera.2011.12.005 *not target outcome*

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*

7 College ter Beoordeling van Geneesmiddelen. Biosimilar geneesmiddel. 2018. [cited 2020 21 February] https://www.cbg-meb.nl/onderwerpen/hv-biosimilar-geneesmiddel. *not target outcome*

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*

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*

20 Melazzini M. Biosimilari: una risorsa per i pazienti e per il sistema sanitario. Agenzia Italiana del Farmaco; [cited 2020 21 February] https://aifa.gov.it/-/biosimilari-una-risorsa-per-i-pazienti-e-per-il-sistema-sanitario. *not target outcome*

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*

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*

13.5 Assessment of publication bias

Figure A 1 Funnel plot to assess publication bias for ACR20

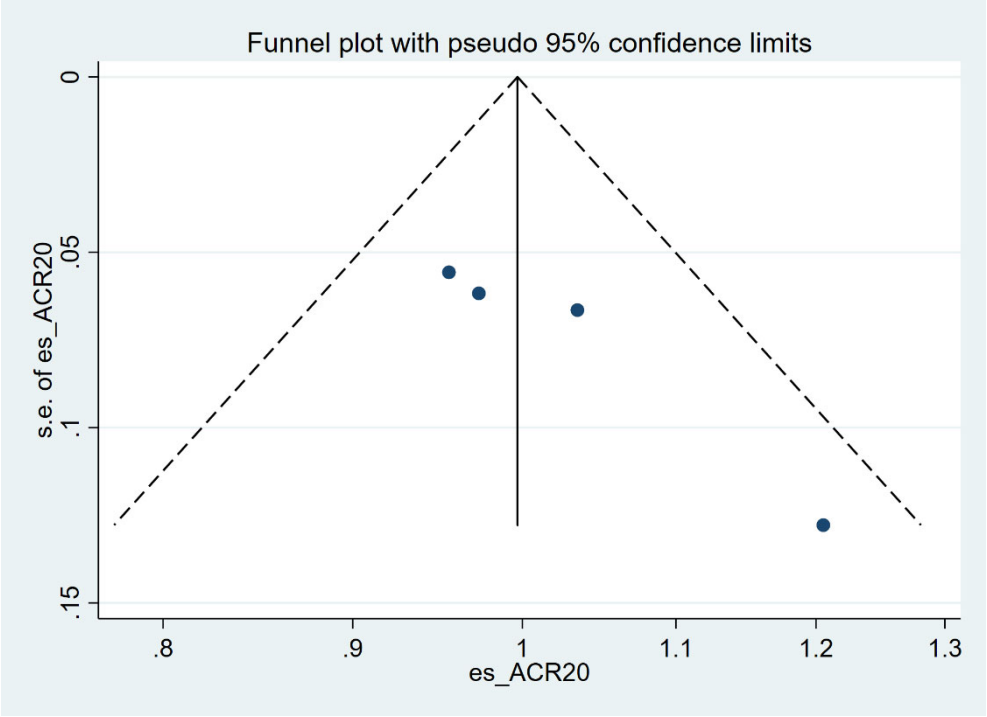


Figure A 2 Funnel plot to assess publication bias for ACR50

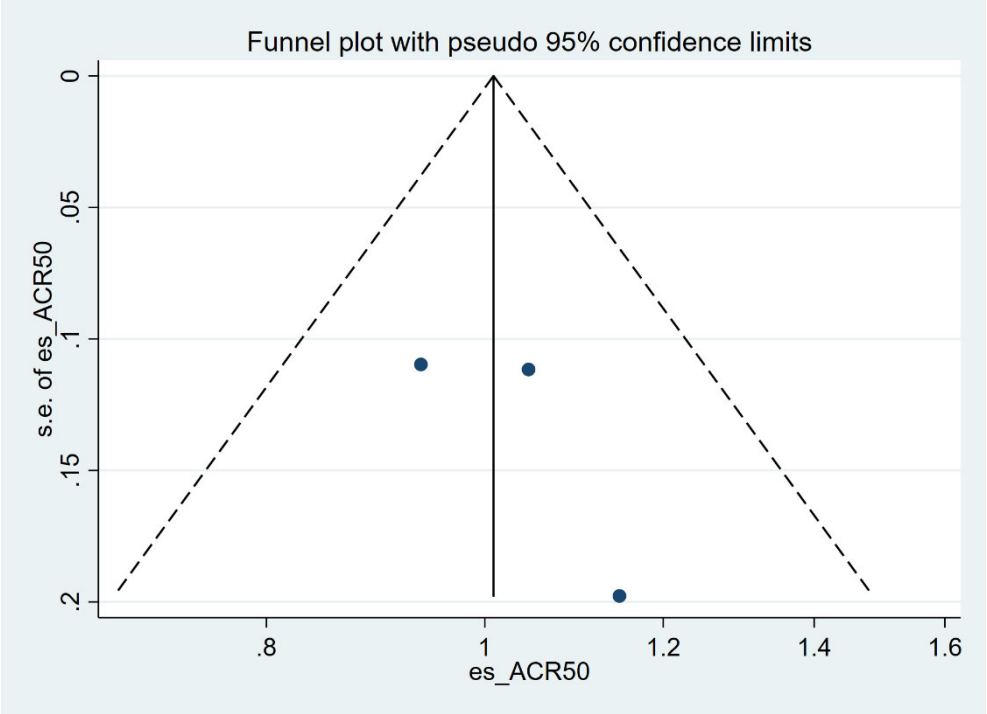


Figure A 3 Funnel plot to assess publication bias for ACR70

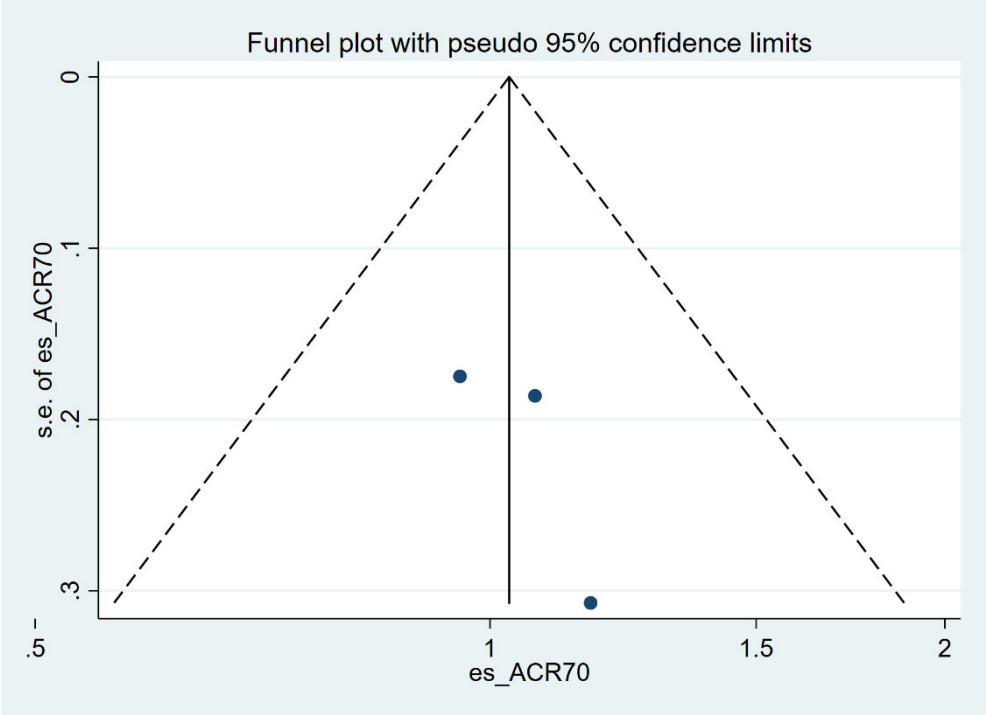


Figure A 4 Funnel plot to assess publication bias for HAQ-DI

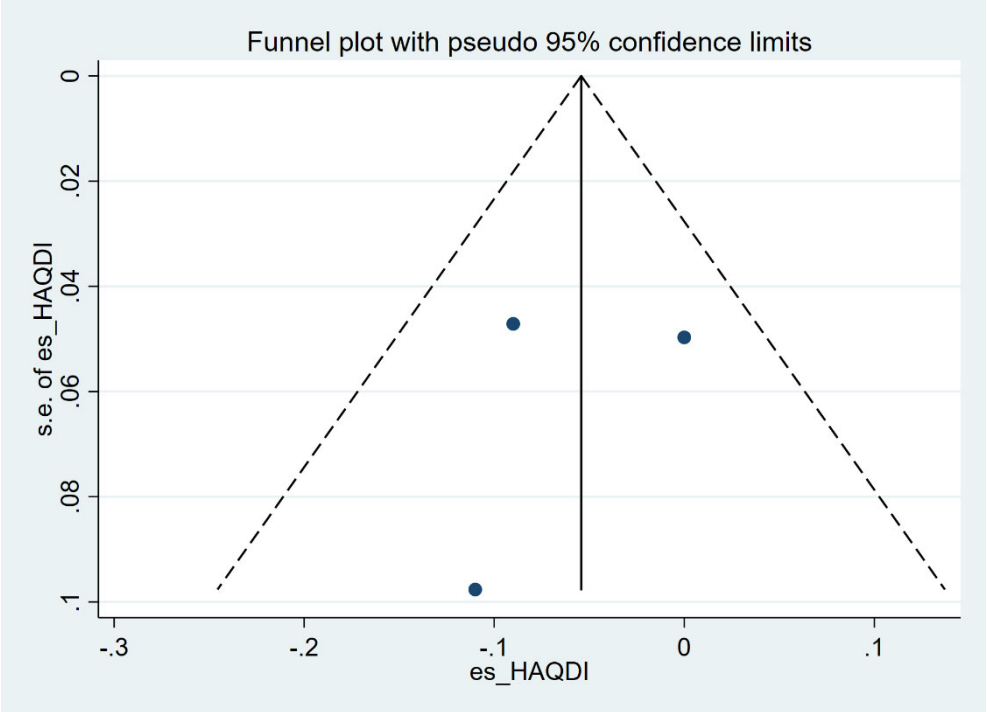
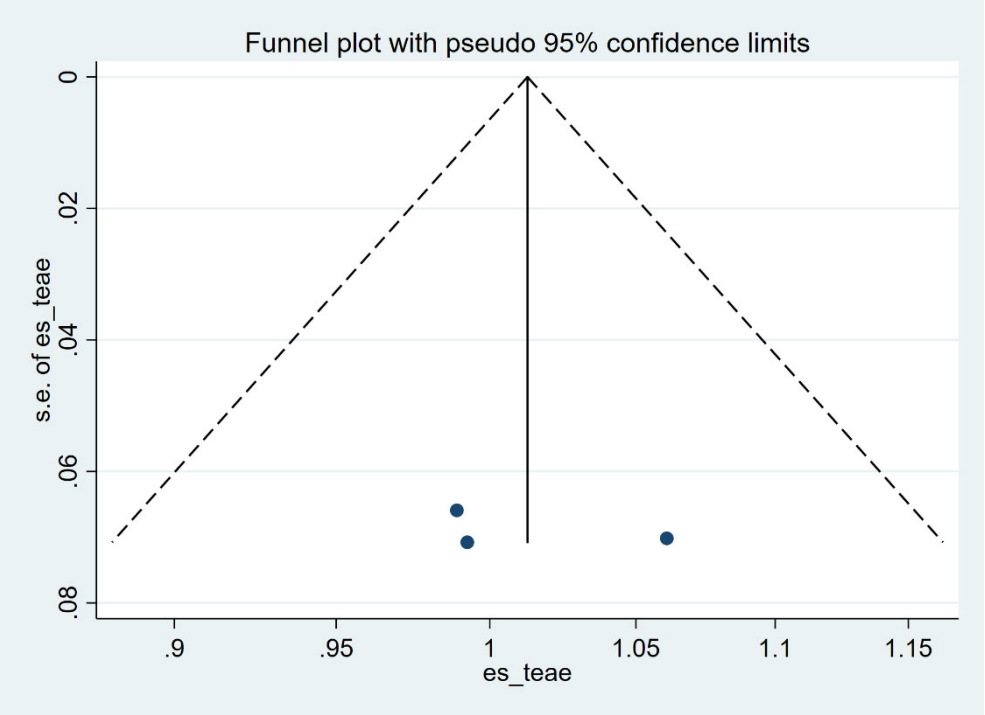


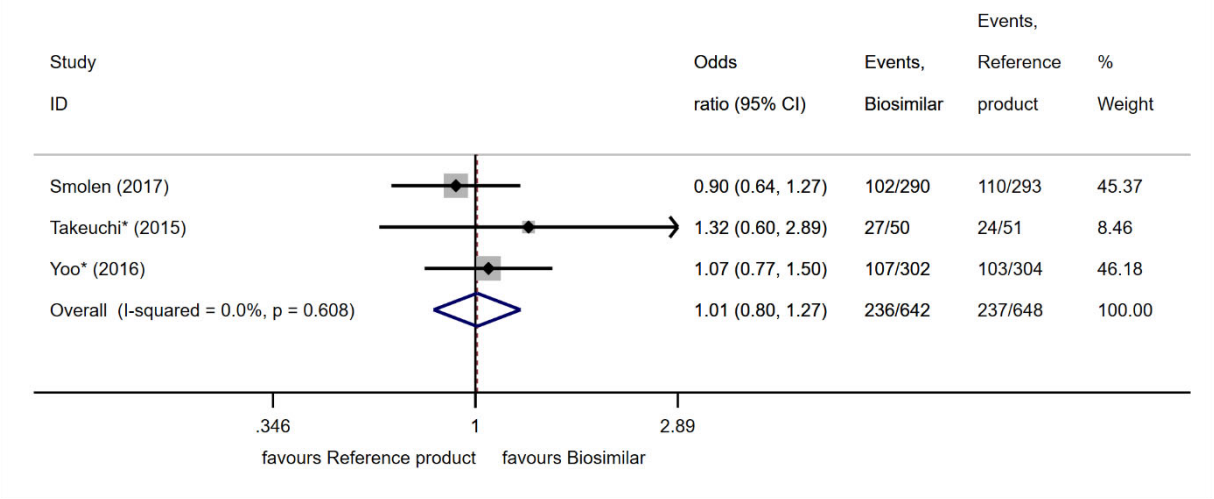
Figure A 5 Funnel plot to assess publication bias for treatment-emergent adverse events (teae)



13.6 Additional information regarding the findings for efficacy and safety

13.6.1 Forest-plot and odds ratios of the meta-analysis for PICO 1

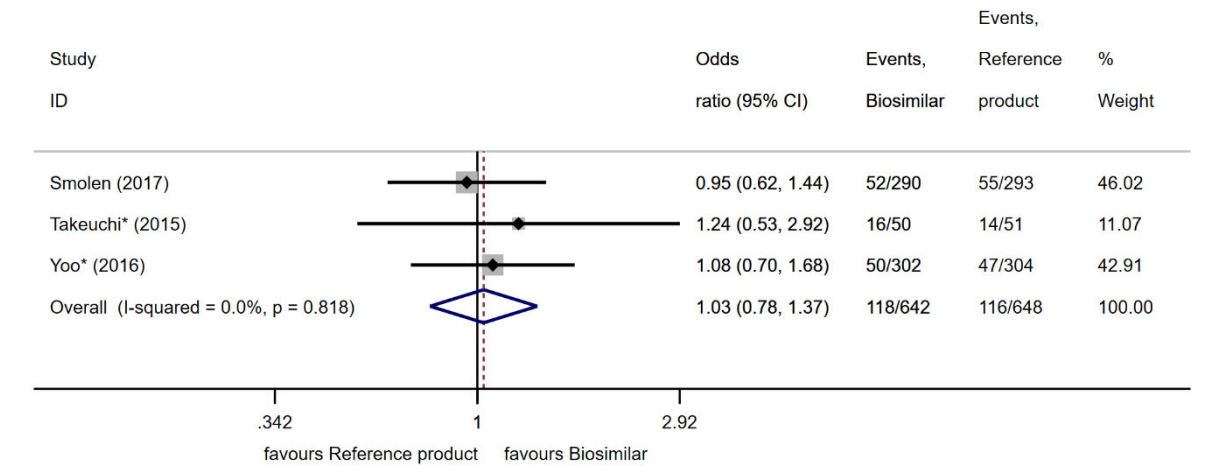
Figure A 6 Forest-plot of ARCR50 after 30 weeks of treatment with reference product compared to biosimilar



The figure presents odds ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland*

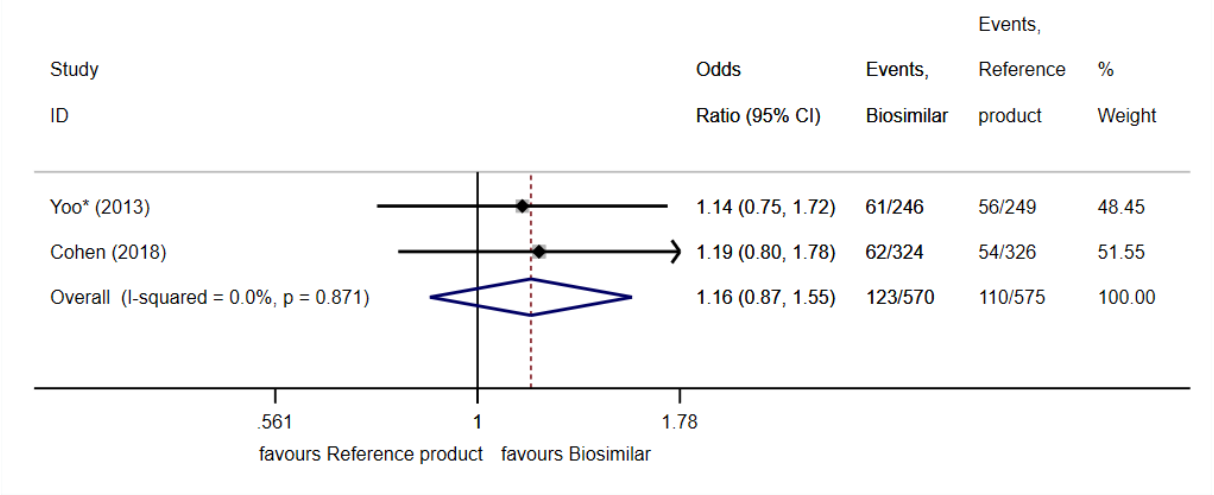
Figure A 7 Forest-plot of ARCR70 after 30 weeks of treatment with reference product compared to biosimilar



The figure presents odds ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland*

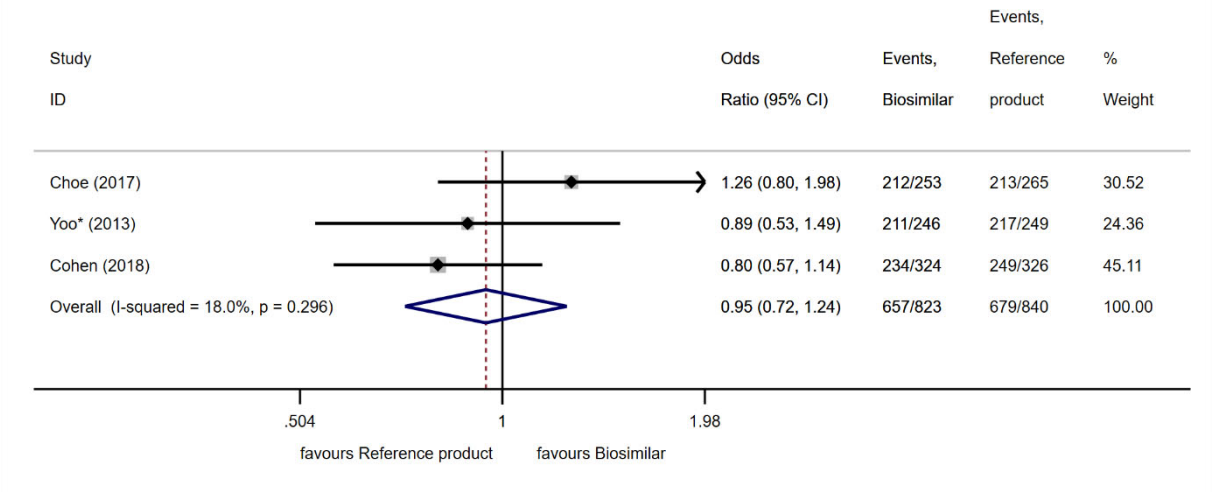
Figure A 8 Forest-plot of DAS28-CRP remission after 30 weeks of treatment with reference product compared to biosimilar



The figure presents odds ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland*

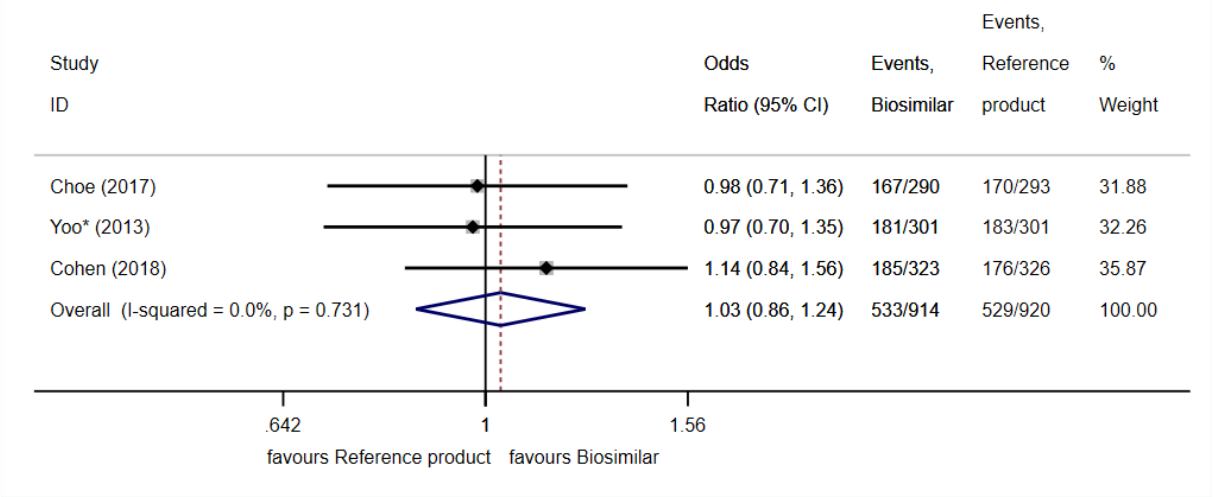
Figure A 9 Forest-plot of EULAR response after 30 weeks of treatment with reference product compared to biosimilar



The figure presents odds ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland*

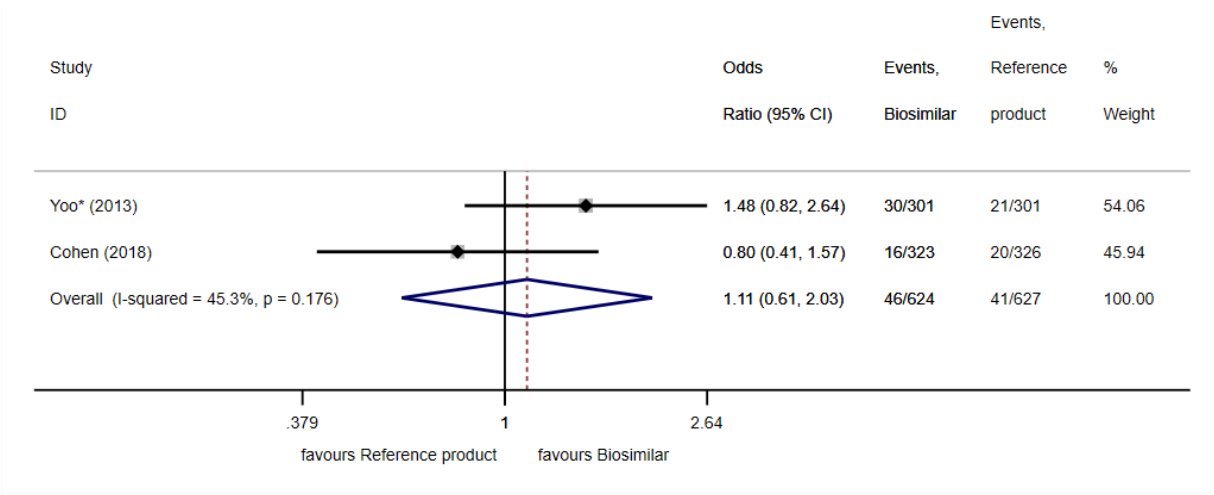
Figure A 10 Forest-plot of treatment-emergent adverse events after 30 weeks of treatment with reference product compared to biosimilar



The figure presents odds ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland*

Figure A 11 Forest-plot of treatment-emergent serious adverse events after 30 weeks of treatment with reference product compared to biosimilar



The figure presents odds ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland*

13.6.2 Table of clinical efficacy of PICO 1 for the 54 weeks follow-up (critical outcomes)

Table A 1 Clinical efficacy at the 54 weeks follow-up

Study	-	0	+	Follow-up	Reference product	Biosimilar
ACR20 (Proportion of patients who achieved an ACR20 response rate)						
Smolen 2017		X		54	68.40%	64.48%
Takeuchi* 2015		X		54	49.02%	64.00%
Yoo* 2016		X		54	52.00%	57.00%
ACR50 (Proportion of patients who achieved an ACR50 response rate)						
Smolen 2017		X		54	38.70%	40.80%
Takeuchi* 2015		X		54	31.37%	50.00%
Yoo* 2016		X		54	31.60%	33.10%
ACR70 (Proportion of patients who achieved an ACR70 response rate)						
Smolen 2017		X		54	23.10%	23.20%
Takeuchi* 2015		X		54	13.73%	42.00%
Yoo* 2016		X		54	15.20%	16.20%
HAQ-DI (Change from baseline ± standard deviation [where specified])						
Smolen 2017		X		54	-0.5	-0.5
Takeuchi* 2015		X		54	-0.25 ± 0.47	-0.54 ± 0.59
Yoo* 2016		X		54	-0.53 ± 0.6	-0.61 ± 0.61
SDAI (Change from baseline ± standard deviation [where specified])						
Takeuchi* 2015		X		54	-14.14 ± 12.24	-18.43± 15.77
Yoo* 2016		X		54	-24.6	-26.3

CDAI (Change from baseline ± standard deviation [where specified])						
Takeuchi* 2015		X		54	-13.66 ± 11.51	-17.39 ± 14.82
Yoo* 2016		X		54	-24.0	-25.7
EULAR (Proportion of patients who achieved a moderate or good EULAR response)						
Yoo* 2016		X		54	82.49%	87.39%
DAS28-CRP						
Takeuchi* 2015		X		54	-1.431 ± 1.346	-2.077 ± 1.65
Yoo* 2016		X		54	-2.2	-2.3

-: favours reference product, 0: no difference, +: favours biosimilar

** Studies investigated biosimilars approved in Switzerland*

13.6.3 Table of safety of PICO 1 for the 54 weeks follow-up (critical outcomes)

Table A 2 Safety at the 54 weeks follow-up

Study	-	0	+	Follow-up	Reference product	Biosimilar
Treatment-emergent adverse events (Proportion of patients)						
Smolen 2017		X		54	65.19%	61.72%
Yoo* 2016		X		54	70.33%	70.53%
Treatment-emergent serious adverse events (Proportion of patients)						
Smolen 2017		X		54	10.58%	10.00%
Yoo* 2016		X		54	10.33%	13.91%

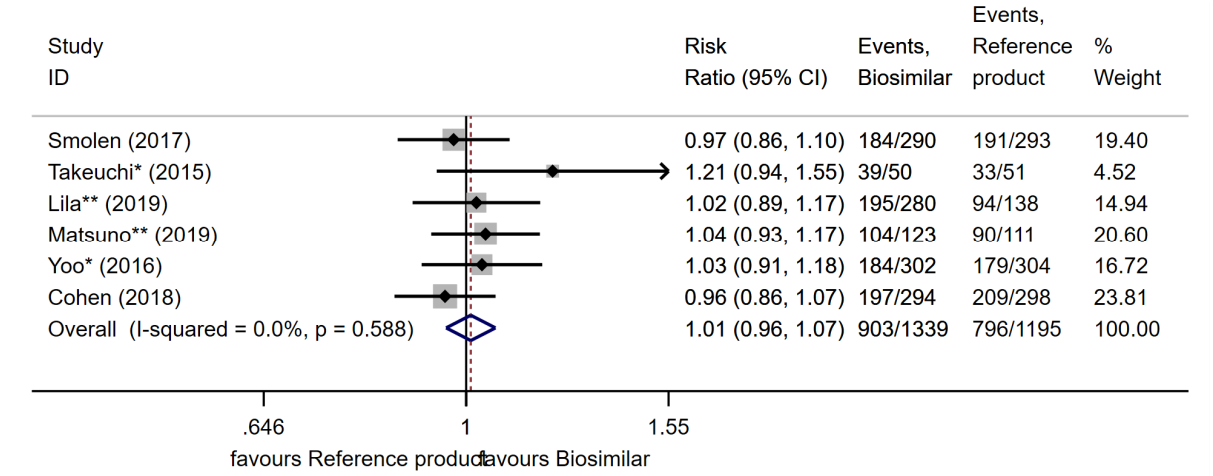
-: favours reference product, 0: no difference, +: favours biosimilar

** Studies investigated biosimilars approved in Switzerland*

13.6.4 Forest-plot of the extended meta-analysis for PICO 1

The following graphs show the result of the meta-analysis for PICO 1 with all published RCTs included, also the ones which analyses biosimilars which are approved only in Russia and India or Japan.

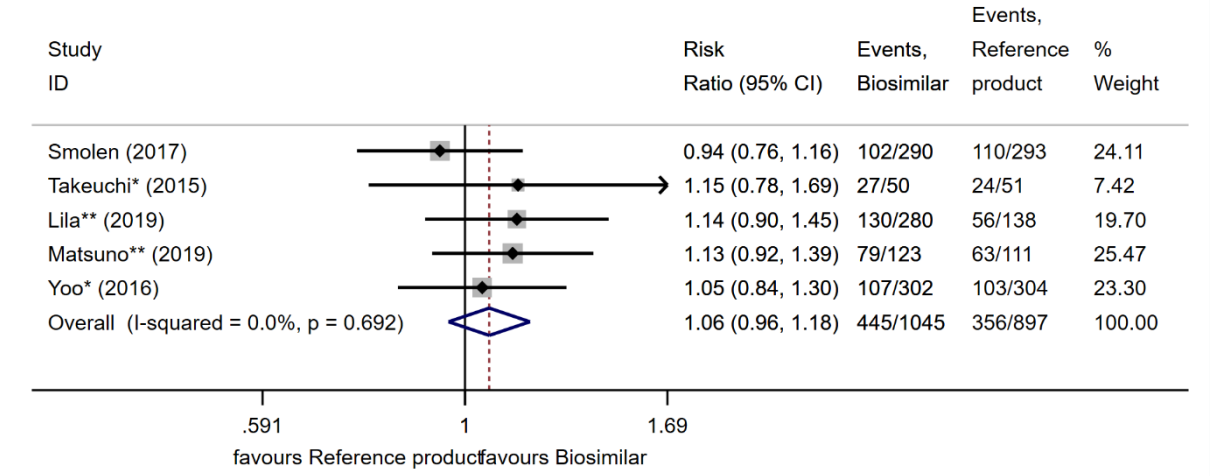
Figure A 12 Forest-plot of ARCR20 after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland. ** Studies investigated biosimilars approved only in Russia and India or Japan*

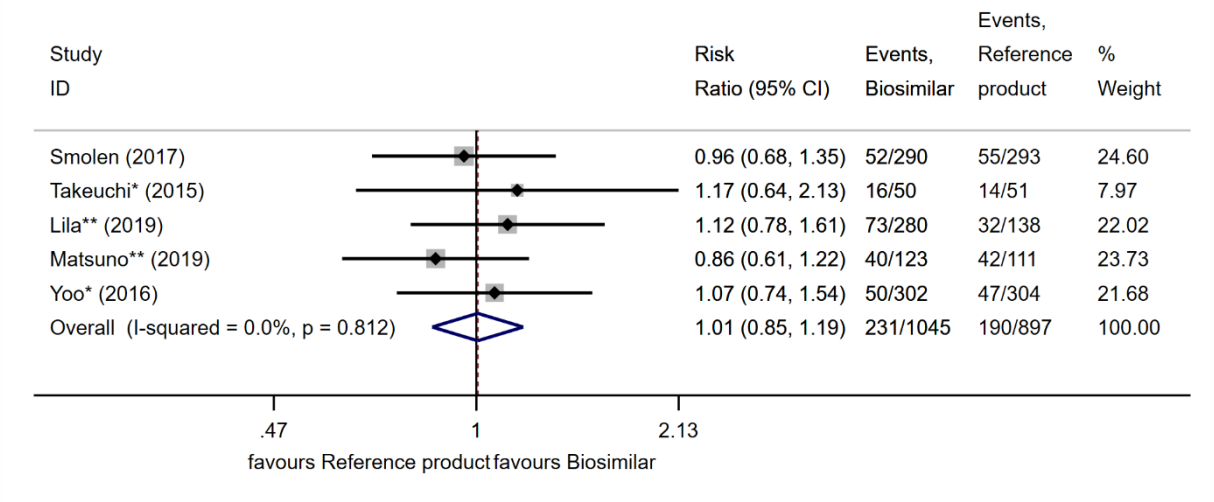
Figure A 13 Forest-plot of ARCR50 after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland. ** Studies investigated biosimilars approved only in Russia and India or Japan*

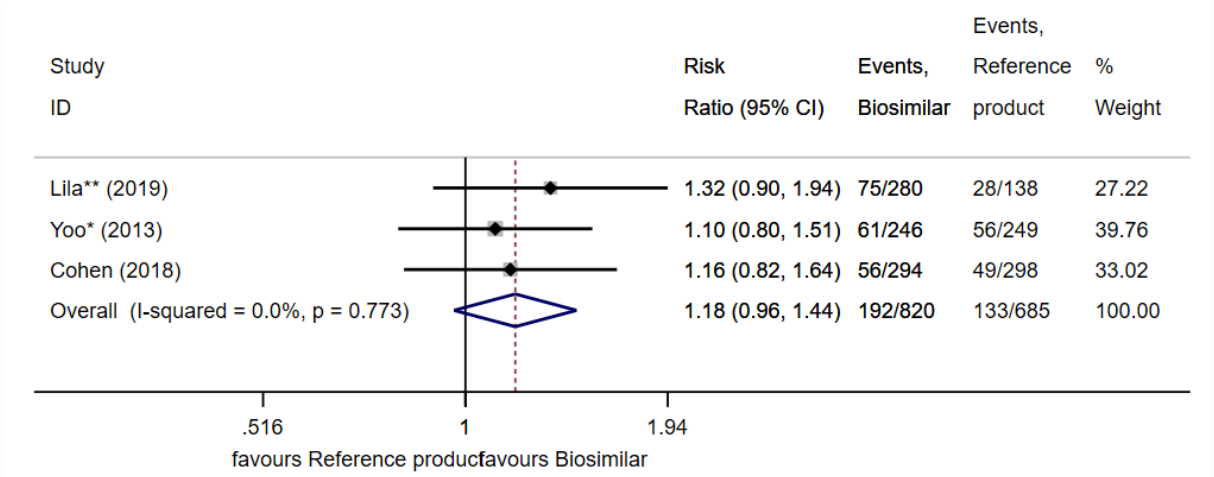
Figure A 14 Forest-plot of ARCR70 after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland. ** Studies investigated biosimilars approved only in Russia and India or Japan*

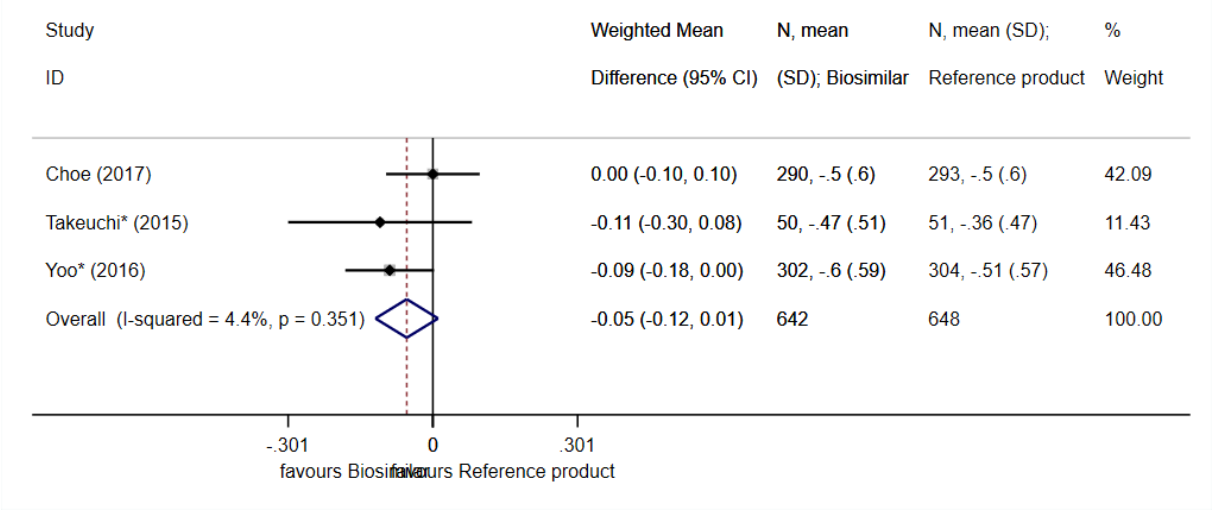
Figure A 15 Forest-plot of DAS28-CRP remission after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland. ** Studies investigated biosimilars approved only in Russia and India or Japan*

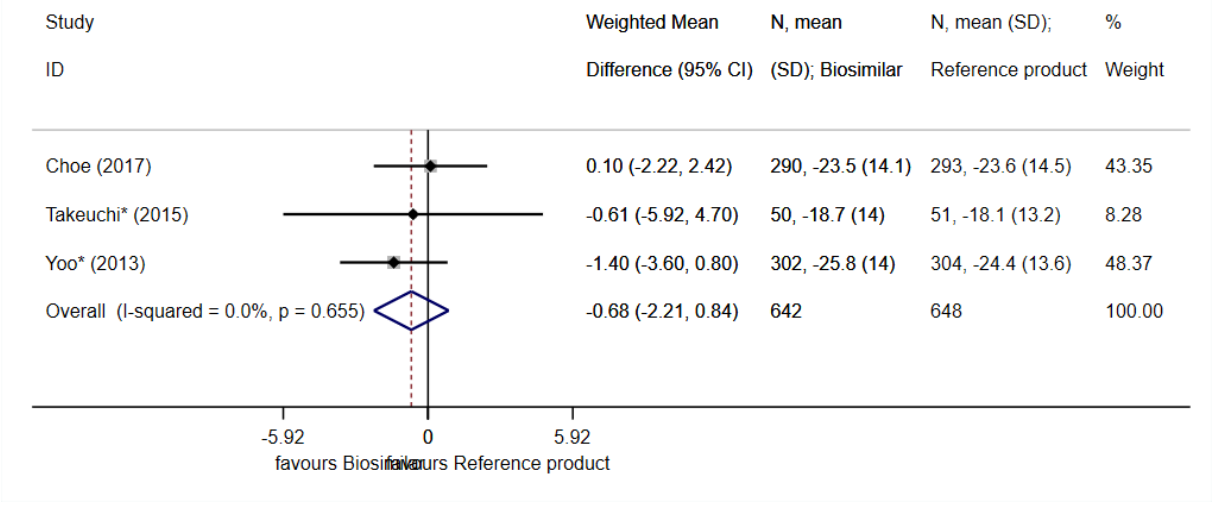
Figure A 16 Forest-plot of HAQ-DI after 30 weeks of treatment with reference product compared to biosimilar



The figure presents weighted mean differences and its 95% confidence interval (95% CI) between treatments. If CI contains the value 0 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland. ** Studies investigated biosimilars approved only in Russia and India or Japan*

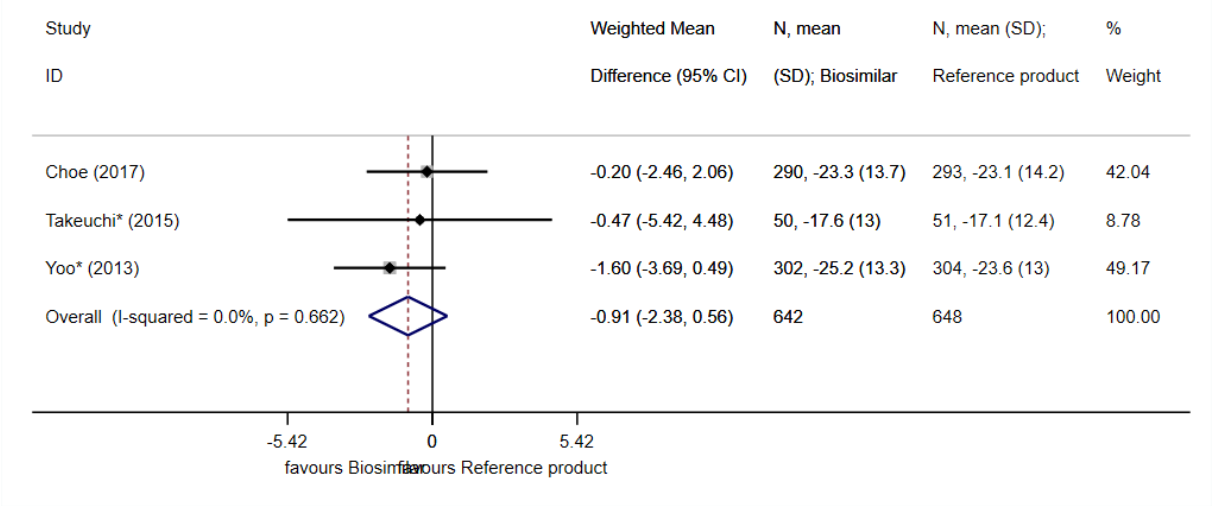
Figure A 17 Forest-plot of SDAI after 30 weeks of treatment with reference product compared to biosimilar



The figure presents weighted mean difference and its 95% confidence interval (95% CI) between treatments. If CI contains the value 0 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland. ** Studies investigated biosimilars approved only in Russia and India or Japan*

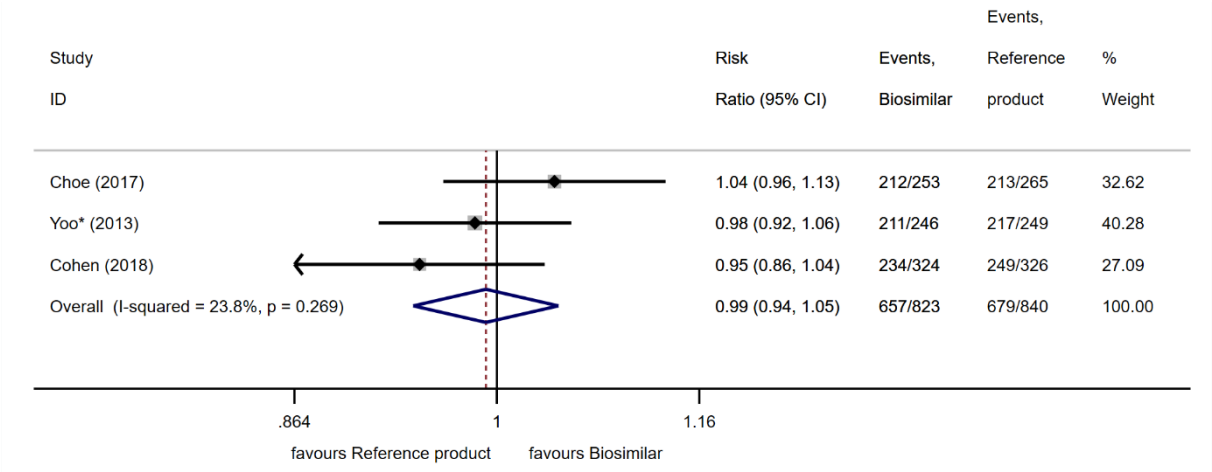
Figure A 18 Forest-plot of CDAI after 30 weeks of treatment with reference product compared to biosimilar



The figure presents weighted mean difference and its 95% confidence interval (95% CI) between treatments. If CI contains the value 0 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland. ** Studies investigated biosimilars approved only in Russia and India or Japan*

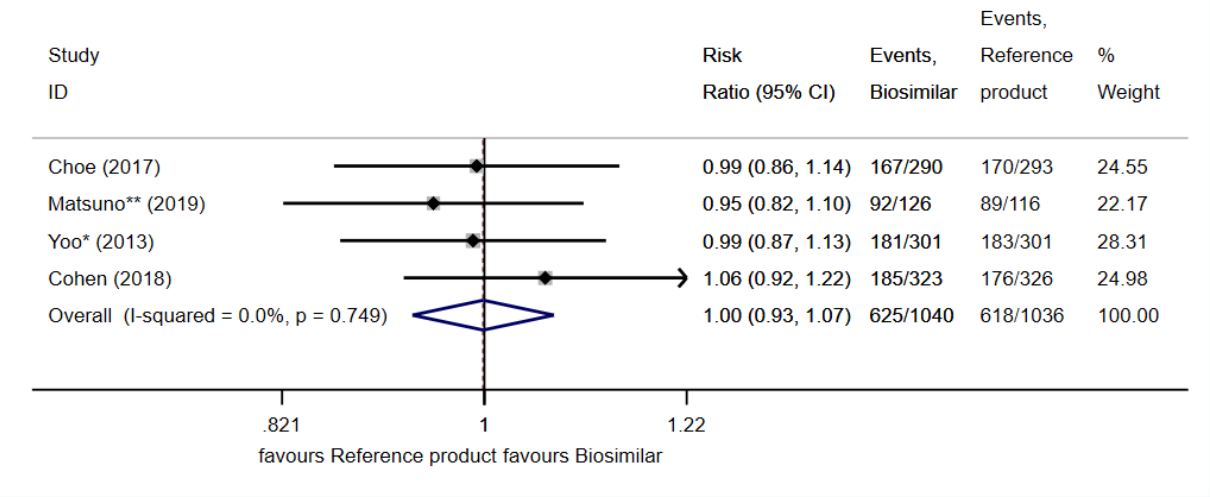
Figure A 19 Forest-plot of EULAR response after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant.

** Studies investigated biosimilars approved in Switzerland. ** Studies investigated biosimilars approved only in Russia and India or Japan*

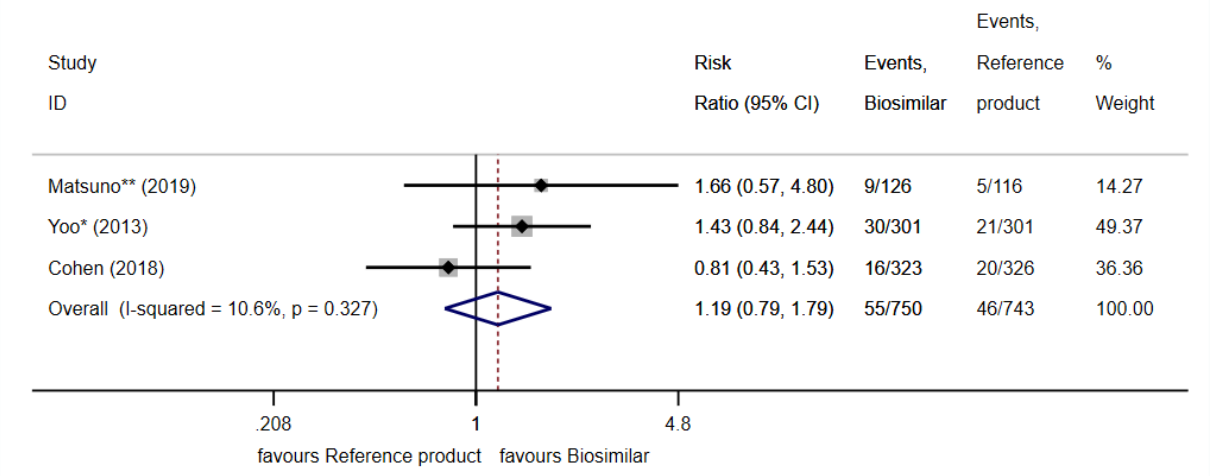
Figure A 20 Forest-plot of treatment-emergent adverse events after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant. AE: adverse event.

** Studies investigated biosimilars approved in Switzerland. ** Studies investigated biosimilars approved only in Russia and India or Japan*

Figure A 21 Forest-plot of treatment-emergent serious adverse events after 30 weeks of treatment with reference product compared to biosimilar



The figure presents risk ratios and its 95% confidence interval (95% CI) between treatments. If CI contains the value 1 the difference between treatments is not statistically significant. AE: adverse event.

** Studies investigated biosimilars approved in Switzerland. ** Studies investigated biosimilars approved only in Russia and India or Japan*

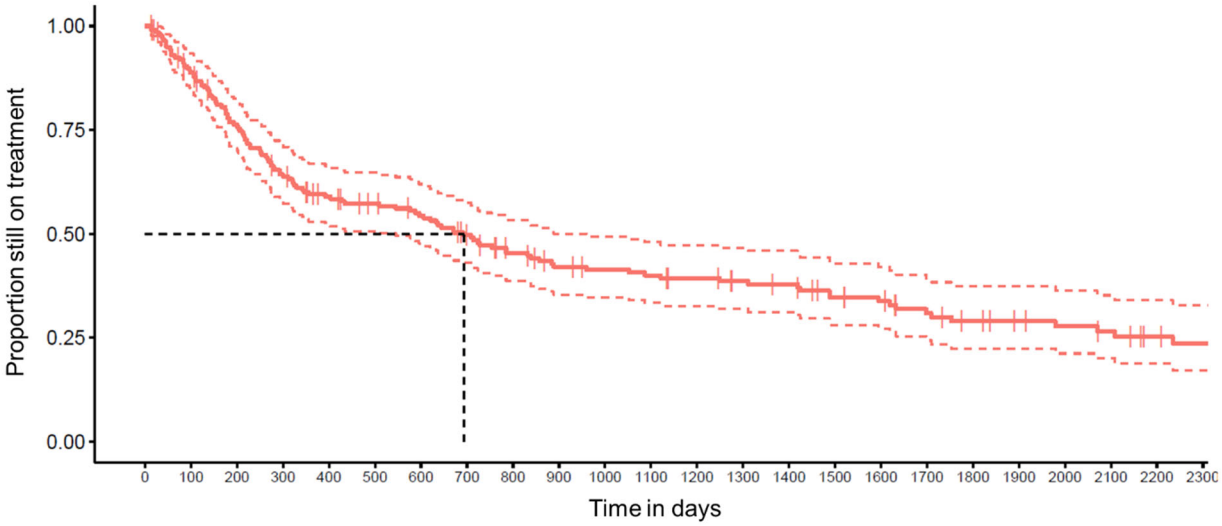
13.7 Details HE studies quality assessment

Appendix table 6 Detailed results per study of HE studies quality assessment using the CHEC checklist

CHEC list item	Aladul 2019	Aladul 2017	Beck 2017	Curtis 2019	Gibofsky 2019	Glintborg 2018	Jha 2015	Kanters 2017	Lucioni 2015	Mansell 2019	Yazdany 2018	Crosby 2020	Ghabri 2020
Is the study population clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Sub	Yes	Yes
Are competing alternatives clearly described?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Sub	Yes	Yes	Yes	Yes
Is a well-defined research question posed in answerable form?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes	Yes	Yes	Yes	Yes
Is the economic study design appropriate to the stated objective?	Sub	Sub	Sub	Sub	Sub	Yes	Sub	Sub	Sub	Sub	Yes	Sub	Yes
Are the structural assumptions and the validation methods of the model properly reported?	Yes	Yes	Yes	Sub	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the chosen time horizon appropriate in order to include relevant costs and consequences?	Yes	Yes	Yes	Yes	Sub	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Is the actual perspective chosen appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are all important and relevant costs for each alternative identified?	Sub	Sub	Yes	Sub	Yes	No	No	Sub	No	No	No	Sub	Yes
Are all costs measured appropriately in physical units?	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
Are costs valued appropriately?	Sub	Yes	Yes	Sub	Yes	No	Yes	Sub	Sub	Sub	Yes	Yes	Yes
Are all important and relevant outcomes for each alternative identified?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
Are all outcomes measured appropriately?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
Are outcomes valued appropriately?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
Are all future costs and outcomes discounted appropriately?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Sub	Yes	Sub	Sub	Sub	No	Sub	Sub	Sub	No	Yes	Yes	Yes
Do the conclusions follow from the data reported?	Yes	Yes	Yes	Sub	Yes	Sub	Yes	Sub	Yes	Yes	Sub	yes	Yes
Does the study discuss the generalizability of the results to other settings and patient/client groups?	Yes	Yes	Yes	Sub	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes
Does the article/report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Yes	No	No	No	No	No	No	No	No	No	Sub	No
Are ethical and distributional issues discussed appropriately?	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	No	No	No

13.8 Additional data for health economic evaluation

Figure A 22 Kaplan-Meier curve drug retention RA patients on infliximab in SCQM



Source: SCQM[177]

Abbreviation: SCQM, Swiss Clinical Quality Management Registry

Appendix table 7 physician and lab costs

Tarmed position	Description	AL (in TP)	TL (in TP)	CHF using average tax point value	Sources
Physician costs					
00.1580	Behandlung durch den Facharzt für Rheumatologie, pro 5 Min.	10.42	9.34	17.21	Tarmed Version 01.09; https://eligo.ch/Tarmed-Taxpunktwerte.html
Lab costs					
00.0715	Punktion, venös, zwecks Blutentnahme, jede Lokalisation durch nichtärztliches Personal	-	8.19	7.13	Tarmed Version 01.09; https://eligo.ch/Tarmed-Taxpunktwerte.html
1020.00	Alanin-Aminotransferase (ALAT)			2.50	AL
1027.00	Alkalische Phosphatase			2.50	AL
1093.00	Aspartat-Aminotransferase (ASAT)			2.50	AL
1245.00	C-reaktives Protein (CRP)			10.0	AL
1341.00	Gamma-Glutamyl-Transferase (GGT)			2.50	AL
1371.00	Hämatogramm II: Erythrozyten, Hämoglobin, Hämatokrit, Indices, Leukozyten und Thrombozyten			9.00	AL
1509.00	Kreatinin			2.50	AL
1666.00	Blutkörperchensenkungsreaktion (BSR)			1.00	AL
			Sum lab	39.63	

Abbreviations: AL, «Ärztliche Leistung»; TL, «Technische Leistung»; TP, tax point

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

Appendix table 8 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
#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

13.10 Studies excluded from searches for evidence on ELSO outcome searches

1 Ahmed I, Kaspar B, Sharma U. Biosimilars: impact of biologic product life cycle and European experience on the regulatory trajectory in the United States. Clin Ther 2012;34:400–19. 10.1016/j.clinthera.2011.12.005 *not target outcome*

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*

7 College ter Beoordeling van Geneesmiddelen. Biosimilar geneesmiddel. 2018. [cited 2020 21 February] https://www.cbg-meb.nl/onderwerpen/hv-biosimilar-geneesmiddel. *not target outcome*

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*

20 Melazzini M. Biosimilari: una risorsa per i pazienti e per il sistema sanitario. Agenzia Italiana del Farmaco; [cited 2020 21 February] https://aifa.gov.it/-/biosimilari-una-risorsa-per-i-pazienti-e-per-il-sistema-sanitario. *not target outcome*

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*

13.11 Evidence table ELSO

Appendix table 9 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[114]	No	No info	Real-world experience/plans	Canada	Organisational
Dylst *et al.*, 2014[228]	No	No	Real-world experience/plans	Belgium	Organisational
Jensen *et al.*, 2019[231]	No info	No info	Real-world experience/plans	Denmark	Organisational
Mehr and Brook, 2017[245]	Yes	No	Real-world experience/plans	United States	Organisational
Moorkens *et al.*, 2019[115]	Yes	Yes	Real-world experience/plans	Sweden	Organisational
Moorkens *et al.*, 2019[116]	Yes	Yes	Real-world experience/plans	Sweden	Organisational
Rémuzat *et al.*, 2017[229]	Yes	Yes	Review	Europe	Organisational
Aerts *et al.*, 2014[246]	No	No info	Review	Europe	Legal/regulatory
Agence Nationale de Sécurité du Médicament et des Produits de Santé, 2016[247]	No	Not applicable	Q&A/explanation	France	Legal/regulatory
Agenzia Italiana del Farmaco, 2020[248]	Not applicable	Not applicable	Q&A/explanation	Italy	Legal/regulatory
Agenzia Italiana del Farmaco, 2018[249]	Not applicable	Not applicable	Guidance/position statement	Italy	Legal/regulatory
Al-Sabbagh *et al.*, 2016[250]	No info	Yes	Review	United States/Europe	Legal/regulatory
Bhatt, 2018[251]	No	Yes	Review	United States/Europe	Legal/regulatory
British Columbia Ministry of Health, 2020[252]	Not applicable	Not applicable	Q&A/explanation	Canada	Legal/regulatory
Bundesamt für Sicherheit im Gesundheitswesen, 2019[253]	Not applicable	Not applicable	Q&A/explanation	Austria	Legal/regulatory
Carver *et al.*, 2010[254]	Yes	No info	Review	United States	Legal/regulatory
Center for Drug Evaluation and Research, 2020[255]	Not applicable	Not applicable	Guidance/position statement	United States	Legal/regulatory
Center for Drug Evaluation and Research, 2019[256]	Not applicable	Not applicable	Guidance/position statement	United States	Legal/regulatory
Center for Drug Evaluation and Research, 2019[257]	Not applicable	Not applicable	Q&A/explanation	United States	Legal/regulatory
Center for Drug Evaluation and Research, 2017[258]	Not applicable	Not applicable	Q&A/explanation	United States	Legal/regulatory
Chance, 2018[259]	No	No	Review	United States	Legal/regulatory
Chapman *et al.*, 2016[260]	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[261]	No	No	Review	United States	Legal/regulatory
Christl *et al.*, 2017[262]	Not applicable	No info	Review	United States	Legal/regulatory
College ter Beoordeling van Geneesmiddelen, 2015[263]	Not applicable	Not applicable	Q&A/explanation	Netherlands	Legal/regulatory
Daller, 2016[264]	No info	No info	Review	United States/Europe	Legal/regulatory
Dougherty *et al.*, 2018[265]	No	No info	Review	United States	Legal/regulatory
EMA, 2018[266]	Not applicable	Not applicable	Q&A/explanation	Europe	Legal/regulatory
EMA, 2014[118]	Not applicable	Not applicable	Guidance/position statement	Europe	Legal/regulatory
EMA, 2012[267]	Not applicable	Not applicable	Guidance/position statement	Europe	Legal/regulatory
EMA, 2007[268]	Not applicable	Not applicable	Guidance/position statement	Europe	Legal/regulatory
EMA, 2005[269]	Not applicable	Not applicable	Guidance/position statement	Europe	Legal/regulatory
Endrenyi *et al.*, 2019[270]	No info	No info	Review	United States	Legal/regulatory
Epstein, 2018[271]	Yes	Yes	Review	United States	Legal/regulatory
Falit *et al.*, 2015[272]	Yes	No info	Review	United States	Legal/regulatory
FDA, 2020[273]	Not applicable	Not applicable	Guidance/position statement	United States	Legal/regulatory
Feagan *et al.*, 2014[274]	Yes	No info	Review	Multinational	Legal/regulatory
Fimea, 2015[275]	Not applicable	Not applicable	Guidance/position statement	Finland	Legal/regulatory
Fimea, no date[276]	Not applicable	Not applicable	Guidance/position statement	Finland	Legal/regulatory
Gemeinsamer Bundesausschuss, 2020[277]	Not applicable	Not applicable	Guidance/position statement	Germany	Legal/regulatory
Gitter, 2011[278]	No info	No info	Review	United States	Legal/regulatory
Ha and Kornbluth, 2016[279]	Yes	No info	Review	United States	Legal/regulatory
Health Canada, 2016[280]	Not applicable	Not applicable	Guidance/position statement	Canada	Legal/regulatory
Heinemann *et al.*, 2015[281]	Yes	Yes	Review	Multinational	Legal/regulatory
Heled, 2019[282]	No	Not applicable	Reflections	United States	Legal/regulatory
Hung *et al.*, 2017[283]	Yes	No	Review	United States	Legal/regulatory
Juillard-Condat and Taboulet, 2018[284]	No info	No info	Review	France	Legal/regulatory
Kay, 2011[285]	No	No info	Review	United States	Legal/regulatory

First author, year	CoI for at least one author	Industry funding	Study type	Countries	Domain focus
Kirchhoff *et al.*, 2017[286]	Yes	Yes	Review	United States	Legal/regulatory
Lemery *et al.*, 2017[287]	No	No	Review	United States	Legal/regulatory
Li and Lobaina, 2017[288]	Yes	No info	Review	United States	Legal/regulatory
Lucio, 2018[289]	Yes	Yes	Review	United States	Legal/regulatory
Ministerio de Sanidad, Consumo y Bienestar Social, 2019[290]	Not applicable	Not applicable	Guidance/position statement	Spain	Legal/regulatory
NHS England, 2017[291]	Not applicable	Not applicable	Guidance/position statement	United Kingdom	Legal/regulatory
NHS England, no date[292]	Not applicable	Not applicable	Q&A/explanation	United Kingdom	Legal/regulatory
Nikolov and Shapiro, 2017[293]	No	No	Review	United States	Legal/regulatory
O'Callaghan *et al.*, 2019[294]	No	No info	Review	Multinational	Legal/regulatory
Olech *et al.*, 2016[295]	Yes	Yes	Review	Multinational	Legal/regulatory
Paradise, 2015[296]	No info	No info	Review	United States	Legal/regulatory
Paul-Ehrlich-Institut, 2019[297]	Not applicable	Not applicable	Guidance/position statement	Germany	Legal/regulatory
Rahalkar *et al.*, 2018[298]	No	No info	Review	Multinational	Legal/regulatory
Rathore and Bhargava, 2020[299]	No	No	Review	Multinational	Legal/regulatory
Rémuzat *et al.*, 2017[230]	Yes	Yes	Review	Europe	Legal/regulatory
Renwick *et al.*, 2016[300]	No	No info	Review	Multinational	Legal/regulatory
Scott *et al.*, 2015[301]	No info	No info	Review	Canada	Legal/regulatory
Sowinski-Raff, 2018[302]	No	No info	Review	United States	Legal/regulatory
Statens Legemiddelverk, 2017[303]	Not applicable	Not applicable	Guidance/position statement	Norway	Legal/regulatory
Stevenson, 2015[304]	Yes	Yes	Review	United States/Europe	Legal/regulatory
Swartenbroeckx *et al.*, 2014[305]	No info	No info	Review	Europe	Legal/regulatory
Swissmedic, 2020[211]	Not applicable	Not applicable	Guidance/position statement	Switzerland	Legal/regulatory
Swissmedic, 2020[306]	Not applicable	Not applicable	Guidance/position statement	Switzerland	Legal/regulatory
Swissmedic, 2020[307]	Not applicable	Not applicable	Guidance/position statement	Switzerland	Legal/regulatory
Swissmedic, 2020[215]	Not applicable	Not applicable	Guidance/position statement	Switzerland	Legal/regulatory
Therapeutic Goods Administration, 2018[308]	Not applicable	Not applicable	Guidance/position statement	Australia	Legal/regulatory

First author, year	CoI for at least one author	Industry funding	Study type	Countries	Domain focus
Tsiftsoglou *et al.*, 2013[309]	No	No info	Review	Multinational	Legal/regulatory
Tu *et al.*, 2019[310]	No	No	Reflections	Multinational	Legal/regulatory
Wang and Chow, 2012[311]	No info	No	Review	Multinational	Legal/regulatory
Webster and Woollett, 2017[312]	No	No	Reflections	Multinational	Legal/regulatory
World Health Organization, 2009[313]	Not applicable	Not applicable	Guidance/position statement	Multinational	Legal/regulatory
Wong *et al.*, 2017[314]	No	No	Review	United States	Legal/regulatory
Knoepffler, 2016[201]	No info	No info	Reflections	Multinational	Ethical
Murdoch and Caulfield, 2020[200]	No info	No info	Review	Canada	Ethical
Pipalava *et al.*, 2019[199]	No info	Yes	Review	United States/Europe	Ethical

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