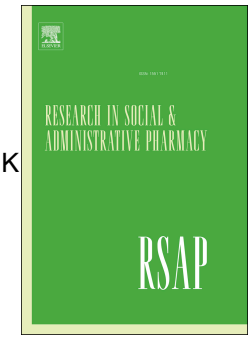
Accepted Manuscript



The effect of new biosimilars in rheumatology and gastroenterology specialities on UK healthcare budgets: Results of a budget impact analysis

Mohammed I. Aladul, Raymond W. Fitzpatrick, Stephen R. Chapman

PII: S1551-7411(17)30978-6

DOI: 10.1016/j.sapharm.2018.05.009

Reference: RSAP 1064

To appear in: *Research in Social & Administrative Pharmacy*

Please cite this article as: 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, *Research in Social & Administrative Pharmacy* (2018), doi: 10.1016/j.sapharm.2018.05.009.

The effect of new biosimilars in rheumatology and gastroenterology specialities on UK healthcare budgets: Results of a budget impact analysis

Running heading: **The impact of adoption of new biosimilars on NHS budget**

Mohammed I Aladul[1,2], Raymond W Fitzpatrick[1], Stephen R Chapman[1*]

[1] School of Pharmacy, Keele University, Hornbeam Building, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

[2] School of Pharmacy, University of Mosul, Mosul, Nineveh, Iraq.

[*] Correspondence to: Stephen R Chapman

School of Pharmacy, Keele University, Hornbeam Building 3.06, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

Tel: +44 (0)1782 734131

Fax: +44 (0)1782 733326

E-mail: s.r.chapman@keele.ac.uk

ORICD: 0000-0002-0326-7742

Compliance with ethical standards

Funding: This study was not funded by any organisation and the researchers are independent of any funding bodies.

Conflict of Interest: Mohammed I Aladul, Raymond W Fitzpatrick, Stephen R Chapman declare that they have no conflict of interest.

Informed consent: Written and verbal consents were obtained from all individual participants included in the study.

Ethical approval: This study approved by the Independent Peer Review Committee at Keele University and the Health Research Authority.

Contributors: All authors have contributed to this study and all authors reviewed and approved the final version of the manuscript. MIA participated in the study design, data collection, and interpretation of results, prepared the manuscript draft, and performed all analytical testing and manuscript review. RWF and SRC participated in the study design and reviewed the manuscript and corrected the final version of the manuscript.

Acknowledgments

Mohammed Aladul was sponsored by the Higher Committee for Education Development in Iraq.

The effect of new biosimilars in rheumatology and gastroenterology specialities on UK healthcare budgets: Results of a budget impact analysis

Abstract

Background: The approval of new biosimilars of infliximab, etanercept and adalimumab by the European Medicines Agency is expected to produce further cost savings to the healthcare system budget.

Objectives: This study aimed to estimate the budget impact of the introduction of new biosimilars Flixabi®, Erelzi®, Solymbic®, Amgevita® and Imraldi® in rheumatology and gastroenterology specialities in the UK.

Methods: A published budget impact model was adapted to estimate the expected cost savings following the entry of new biosimilars Flixabi®, Erelzi®, Solymbic®, Amgevita® and Imraldi® in the UK over three-year time horizon. This model was based on retrospective market shares of biologics used in rheumatology and gastroenterology which were derived from DEFINE Software and healthcare professional perspectives.

Results: The model predicted that infliximab and etanercept biosimilars would replace their corresponding reference agents by 2020. Adalimumab biosimilars were predicted to achieve 19% of the rheumatology and gastroenterology market by 2020. Without the introduction of further biosimilars, the model predicted a reduction in expenditure of £44 million on biologics over the next three years. With the entry of Flixabi®, Erelzi®, Solymbic®, Amgevita® and Imraldi® the model estimates cumulative savings of £285 million by 2020.

Conclusions: The introduction of new infliximab, etanercept and adalimumab biosimilars will be associated with considerable cost savings and have a substantial favourable impact on the UK NHS budget. The number of biosimilars and time of entry of is critical to create competition which will result in maximum cost savings.

Key points

• Previous budget impact analyses predicted a considerable cost savings from the introduction of infliximab and etanercept biosimilars.

• This budget impact analysis estimated the impact of the introduction of new (upcoming) biosimilars in rheumatology and gastroenterology specialities in UK.

• This budget impact analysis is unique in that it uses market reaction to previously marketed biosimilars from retrospective (real-life) data and healthcare professionals' perspectives.

Keywords

Budget impact analysis; biosimilar; rheumatology; gastroenterology

1. Introduction

Rheumatic disorders (RD) including rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PA), and inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory autoimmune diseases. According to the National Rheumatoid Arthritis Society and the British Gastroenterology Association 690,000 and 240,000 people in the UK are living with RD and IBD respectively [1, 2]. RA is the leading cause of pain and disability, costing the National Health Service (NHS) £5 billion a year [1]. The additional cost to the economy of sick leave and work-related disability has been estimated at between £3.8 and £4.75 billion per year [3]. IBD costs the NHS around £900 million annually [4].

Biological disease-modifying antirheumatic drugs (bDMARDs) and biological disease-modifying anti-inflammatory bowel disease drugs (bDMAIDs), as monoclonal antibodies and soluble receptors, are well established as the most effective agents for treating patients with severe RD and moderate to severe IBD and for those unresponsive to conventional agents [5, 6]. Given the nature of RD and IBD, both bDMARDs and bDMAIDs are considered chronic therapy and are often continued indefinitely upon commencement unless there is either loss of response or side effects [7]. bDMARDs, and bDMAIDs are expensive and contribute highly to RD and IBD bills [8].

Biosimilars are potentially cost-effective alternatives to reference biological medicines and represent a cost containment tool to reduce the biologics bill [9]. Up to September 2017, three biosimilars of infliximab (Inflectra® and Remsima®) and etanercept (Benepali®) were in use in the UK for RD and IBD. Recently, an additional infliximab biosimilar (Flixabi®) and an etanercept biosimilar (Erelzi®) received market authorisation in the UK. Three adalimumab biosimilars (Solymbic®, Amgevita® and Imraldi®) were licenced by the European Medicine Agency (EMA) in March and August 2017 and launch is anticipated in the UK market immediately following the patent expiry of branded (reference) adalimumab (Humira®) in October 2018 [10, 11]. The behaviour of the biologics market following the launch of infliximab and etanercept biosimilars suggests that the introduction of adalimumab biosimilars will provoke competition with subsequent savings. A previous survey of healthcare professionals (HCPs) showed that there are subtle differences between specialities views on biosimilars with different uptake patterns [12].

Budget impact analysis (BIA) is an estimation of the potential financial impact of the adoption of a new intervention (medicine) into health systems such as the UK NHS over a short to medium time horizon [13, 14]. BIA provides health service managers and commissioners (payers) with information to support budget planning and effective resources allocation [15].

A survey of the literature revealed that budget impact analyses have been performed to estimate cost savings associated with the entry of infliximab and etanercept biosimilars before and after their market entry at national and international levels [16-25]. The majority of these budget impact analyses were based on third-party payer perspective (public health systems, payers, patients, and healthcare professionals). None of these analyses were conducted on adalimumab biosimilars or the impact of the entry of new infliximab and etanercept biosimilars in RD and IBD markets. Furthermore, none of these studies has factored in the impact of competition on reference biologic and biosimilars prices. To fill this gap in knowledge, the aim of this study was to estimate the potential cost savings associated with the introduction of adalimumab, etanercept and infliximab biosimilars (Solymbic®, Amgevita®, Imraldi®, Erelzi® and Flixabi®) for the treatment of RD and IBD on the NHS budget in the UK for the next three years (2018-2020). As the time horizon for the BIA should be until the proposed drug has reached a stable market share [14], it is expected that adalimumab biosimilars would reach a stable market share by 2020. Since there are already biosimilars of infliximab and etanercept on the market, it is anticipated that the market share for the new biosimilars would be stable before then.

2. Methods

2.1. Healthcare professional perspectives

Healthcare professionals (HCPs) (consultants, pharmacists and nurses) in rheumatology and gastroenterology specialities who are involved in prescribing, managing and procuring biological medicines including biosimilar medicines were asked for the expected price reduction offered by newly launched biosimilars.

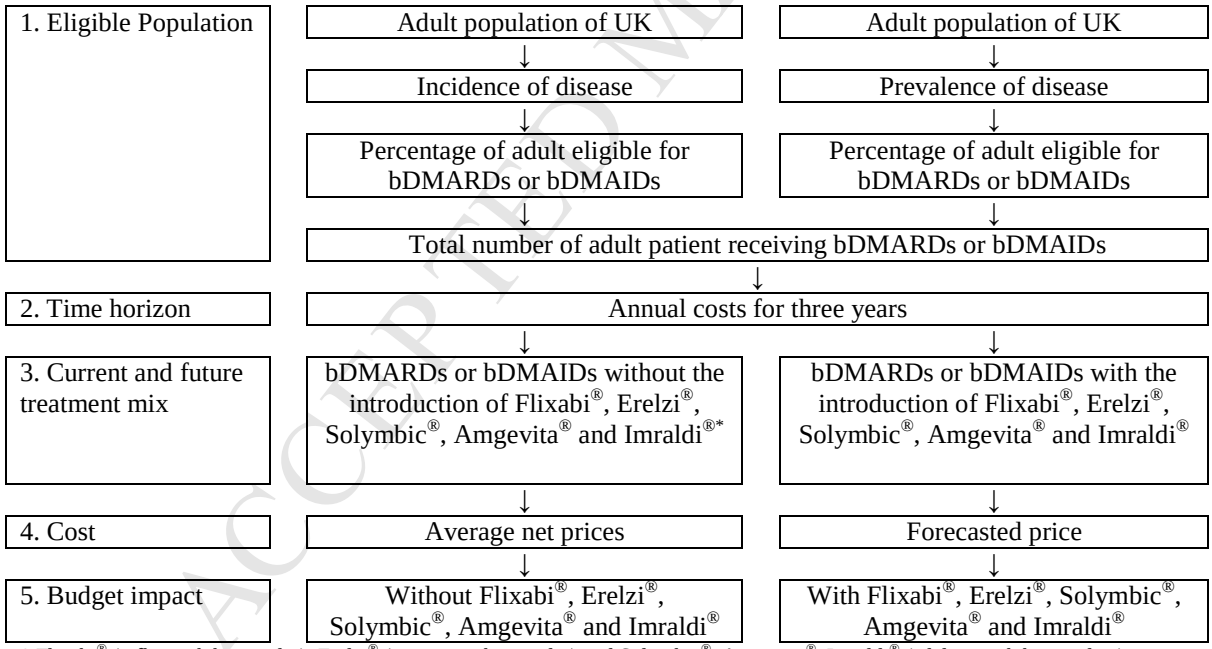
2.2. Budget impact analysis model

A published Microsoft Excel-based static budget impact model developed by Mauskopf et al., [14] was modified and updated to estimate the financial impact of the introduction Solymbic®, Amgevita®, Imraldi® (adalimumab biosimilars), Erelzi® (etanercept biosimilar) and Flixabi® (infliximab biosimilar) for the treatment of RD and Solymbic®, Amgevita®, Imraldi® and Flixabi® for the treatment IBD in the UK. A one-year time horizon (reference case scenario) was built from current (in 2017) real-life market shares and prices for each biological drug (the reference and the biosimilar), in rheumatology and gastroenterology specialities, derived from the DEFINE Software [26]. A three-year time horizon BIA model for the years 2018-2020 was created based on extrapolation of the utilisation trends and costs from data on the market reaction to existing biosimilars of bDMARDs and bDMAIDs. The perspective of HCPs in rheumatology and gastroenterology was also included in the BIA model (Table 1).

2.3. Population

Data on adult population, disease-specific incidence and prevalence, percentage of patients who were eligible to receive bDMARDs and bDMAIDs in the UK were derived from the published literature and NHS reports (Table 2) [27-33]. The size of the adult population in the UK (eligible population) was 50,192,000 with 0.8% annual population growth rate [34]. Applying the eligibility criteria in Table 1 resulted in estimation of 626,847 patients with a rheumatological disease and 230,883 patients with a gastroenterological disease. The estimated number of adult patients receiving biological medicine is the sum of (adult population multiplied by the incidence of a specific disease multiplied by the percentage of eligible patient population for biological treatment (Table 2)) plus (adult population multiplied by the prevalence of a specific disease multiplied by the percentage of eligible patient population for biological treatment (Table 2)).

Table 1 Flow diagram for an analysis of the budget impact of infliximab, etanercept and adalimumab biosimilars in rheumatology and gastroenterology specialities in the UK



* Flixabi® (infliximab biosimilar), Erelzi® (etanercept biosimilar) and Solymbic®, Amgevita®, Imraldi® (adalimumab biosimilars)

Table 2 Percentage of incidence and prevalence of rheumatic disorders and IBD

Population	Ulcerative colitis [27]	Crohn's Disease [28]	Rheumatoid Arthritis [29, 30]	Ankylosing Spondylitis [31, 32]	Psoriatic Arthritis [33]
Prevalence	0.24%	0.20%	0.86%	0.2%	0.15%
Incidence	0.01%	0.01%	0.015%	0.0069%	0.017%
Percentage patient	11.5%*	19%**	10%*	20%*	2.4%*

population eligible for biological treatment					
Estimated total number of adult patients receiving biological treatment	14,603	20,027	43,918	20,770	2,012

* Eligible patient population for biological treatment taken from the literature [refences 27, 30, 32, 33]

** Eligible patient population for biological treatment is the sum of multiplication of percentage of adults with moderate or severe Crohn's disease (40%) multiplied by the percentage of patients in whom conventional treatment is ineffective or where they cannot tolerate it (50%) multiplied by the percentage of adults with moderate or severe Crohn's disease who require anti-tumour necrosis agent (95%) [reference 28]

2.4. Market shares and cost

Retrospective secondary care market shares of bDMARDs (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab) in rheumatology specialities (Figure 1) and bDMAIDs (adalimumab, infliximab, golimumab and vedolizumab) in gastroenterology specialities (Figure 2) were derived from the DEFINE Software from January 2014-October 2017. The DEFINE Software is a NHS prescribing database of medicines usage covering over 90% of acute NHS hospitals as well as Specialist Centres and Mental Health Trusts throughout the UK [26]. The UK Medicine Optimisation Dashboard was also visited to view the percentage of uptake of existing biosimilars and degree of saturation in each Trust [35]. Secondary care prices were the average net prices for each product (reference biologic and biosimilar) across all trusts within the DEFINE Software including value-added tax. Annual acquisition costs only were included in this analysis. Administration and therapy monitoring costs were not included (assumed to be the same) since no switching between different molecules was anticipated. Modelling of the switching was limited to reference biological medicine / biosimilar for the same molecule using utilisation patterns from a previous study [16].

2.5. Scenario analysis

Retrospective market analyses of existing anti-tumour necrosis (TNF) biosimilars (from DEFINE Software) revealed that the UK market reacted in a complex way to the availability of these biosimilars as reference biological products reduced their prices in response to the availability of less expensive biosimilars. The model applied to the forward projection for the three current brands of adalimumab, etanercept and infliximab assumed the same level of discounting, i.e.; 10% reduction in the first year of competition, 20% in the second year [16], 35% in the third year (actual data on infliximab from DEFINE Software in October 2017). For the fourth year a discount of 50% was assumed. For the bDMARDs/bDMAIDs biosimilars, a similar retrospective analysis identified an average 33% discount at launch [16], and continued to decrease in response to competition by 15% per year on average. The model assumed this would plateau at 40% of the biosimilars marketing price at year 5 and beyond. These assumptions were further supported by a report in May 2017, in which Remsima had actually been sold to the NHS at prices 40% - 50% lower than the list price of Remicade® [36]. Despite price reductions of reference biological medicines and biosimilars infliximab and etanercept, the prices of other biologics did not change [16].

Biosimilars penetrated the market gradually, achieving 10% of the molecule market in the first year, 35% in the second year and 65% in the third year [16]. Uptake in the fourth year and beyond was modelled at an average of 90%, based on figures from the commissioning framework for biological medicines report in September 2017 [37].

To examine the impact of the introduction of Flixabi®, Erelzi®, Solymbic®, Amgevita® and Imraldi® on the UK budget the first, reference case, scenario considered a market forecast in which no new biosimilars were launched. Four further sequential analyses were conducted all based on 2017 market share and prices. The first scenario was modelled on only infliximab biosimilar (Flixabi®) entering the market at a discount of 50% compared to existing infliximab biosimilars (Inflectra® and Remsima®) in RD and IBD market (based on actual costs in the DEFINE database at October 2017) (Table 3).

The second scenario (etanercept biosimilar (Erelzi®) entry) assumed at a discount of 10% compared to available etanercept biosimilar (Benepali®) in RD (based on the results of the qualitative interviews with HCPs in

rheumatology). The third scenario (adalimumab biosimilars entry) assumed that adalimumab biosimilars would be available at a discount of 33% compared to branded adalimumab (Humira®) in RD and IBD (based on the previous market behaviour of bDMARDs biosimilars and HCPs opinions). The fourth scenario (all new biosimilars entry) examined the budget impact of the availability of all new biosimilars in RD and IBD at the suggested prices and molecule market shares used in scenarios one to three. Linear regression analysis was used to predicted market shares of existing reference biologic and biosimilar bDMARDs and bDMAIDs uptake patterns and extrapolated forward to 2020 (Table 3).

Table 3 Model assumptions

No.	Model name	Assumptions	Biosimilars entry prices	Total biosimilars market share per molecule	Biosimilars price reduction	Reference annual price reduction
0	Reference case scenario	No new biosimilars were launched	Already in use biosimilars (Remsima, Inflectra and Benepali)	1st year 10% 2nd year 35% 3rd year 60% 4th year 90%	1st year 33% of reference price. 2nd - 4th year 15% reduction per year. 5th year and beyond 40% of the reference price.	1st year 10% 2nd year 20% 3rd year 35% 4th year 50%
1	Infliximab biosimilar case scenario	Entry of Flixabi® to RD and IBD markets	Flixabi® actually marketed at a discount of 50% compared to existing infliximab biosimilars (Inflectra® and Remsima®) in RD and IBD market	1st year 10% 2nd year 35% 3rd year 60% 4th year 90%	2nd - 4th year 15% reduction per year.	Already plateaued at 50%
2	Etanercept biosimilar case scenario	Entry of Erelzi® to RD market	Erelzi® marketed at a discount of 10% etanercept biosimilar (Benepali®) in RD	1st year 10% 2nd year 35% 3rd year 60% 4th year 90%	2nd - 4th year 15% reduction per year.	2nd year 20% 3rd year 35% 4th year 50%
3	Adalimumab biosimilars case scenario	entry of Solymbic®, Amgevita® and Imraldi® to RD and IBD markets	Adalimumab biosimilars marketed at a discount of 33% compared to branded adalimumab (Humira®) in RD and IBD	1st year 10% 2nd year 35% 3rd year 60% 4th year 90%	1st year 33% of reference price. 2nd - 4th year 15% reduction per year. 5th year and beyond 40% of the reference price.	1st year 10% 2nd year 20% 3rd year 35% 4th year 50%
4	All new biosimilars case scenario	Entry of Flixabi®, Erelzi®, Solymbic®, Amgevita® and Imraldi® to RD and IBD markets	Entry of all biosimilars in scenarios one to three,	1st year 10% 2nd year 35% 3rd year 60% 4th year 90%	This the sum modelled prices scenarios 1-3	As in scenarios 1-3

2.6. Sensitivity analysis

One-way sensitivity analyses were used to test the sensitivity of the model assumptions. Parameters varied in the sensitivity analyses included market uptake of biosimilars (±10 %), discount on the price of biosimilars (±10 %), the total number of patients treated with biologics (±10 %) for the fourth (all biosimilars entry) scenario (Figure 3). An internal validation of the model has been performed by the authors.

3. Results

3.1. Market shares

Figures 1 and 2 show retrospective and forecasted market shares of biologics before and after the entry of biosimilars in rheumatology and gastroenterology specialities respectively. During 2014, no bDMARDs/bDMAIDs biosimilars were in use in UK.

Figure 1 shows that the percentage of utilisation of infliximab biosimilars increased gradually from 1% in 2015 to 6% in 2017. The percentage of utilisation of etanercept biosimilar (Benepali®) increased from 3.4% in 2016 to 12.6% in 2017. It would be expected that with the entry of new infliximab and etanercept biosimilars, these would replace their corresponding branded reference products by 2020 rather than existing molecule biosimilars (Figure 1). Similarly, it would be expected following the entry of adalimumab biosimilars in 2018 that these biosimilars would achieve 19.4% of the RD market by 2020.

Interestingly, the RD market share of infliximab (reference biologic and biosimilars) decreased from 12% in 2014 to 9.7% in 2017 and is expected to decrease gradually to 8% by 2020. Similarly, the RD market share of etanercept (reference biologic and biosimilar) decreased from 35% in 2014 to 32% in 2017 and is expected to decrease gradually to 30% by 2020. Therefore, it would be expected that following the introduction of adalimumab biosimilars in 2018, the percentage of utilisation of adalimumab (reference biologic and biosimilars) would decrease from 34% in 2017 to 32% by 2020 (Figure 1). In contrast, the RD market share percentage of golimumab (Simponi®), certolizumab (Cimzia®), tocilizumab (RoActemra®) and abatacept (Orencia®) increased from 18% in 2014 to 25% in 2016 and plateaued in 2017. Our model predicts the market share of these agents would increase gradually to 30% by 2020 (Figure 1).

Figure 2 shows that the percentage of utilisation of infliximab biosimilars increased from 11.5% in 2015 to 43.5% in 2017 in the IBD market. It would be expected that this utilisation would further increase with the entry of new infliximab biosimilar to replace branded infliximab (Remicade®) in the IBD market by 2020. Similarly, it would be expected following the entry of adalimumab biosimilars in 2018 that these biosimilars would achieve 19% of the IBD market by 2020 based on the model described in section 2.5 (Figure 2). In a similar way to the RD market, the IBD market share of infliximab (reference biologic and biosimilars) decreased from 66% in 2014 to 54% in 2017 and is expected to decrease gradually to 48.35% by 2020. Therefore, it would be expected that following the introduction of adalimumab biosimilars in 2018, the IBD market share of adalimumab (reference biologic and biosimilars) would decrease from 36% in 2017 to 31.85% by 2020 (Figure 2).

In contrast, the IBD market share of golimumab (Simponi®) and vedolizumab (Entyvio®) increased from 1.5% in 2014 to 10% in 2017. Our model predicts the percentage of utilisation of these agents would increase gradually to 19.8% by 2020 (Figure 2).

3.2. Scenario analysis

Reference case and biosimilars entry scenarios analyses were performed to examine the budget impact of entry of new biosimilars in RD and IBD markets as described in section 2.5. Scenario findings are presented in Table 4. The reference case model assessed the budget impact if no new biosimilars enter the RD and IBD markets. The cumulative impact of this model was a reduction in expenditure by £48,360,678 in RD and an increase of £4,359,509 in IBD for the next three years.

Flixabi®, Erelzi® and adalimumab biosimilars entry models assessed the budget impact of the entry of each biosimilar separately in the RD and IBD markets. The impact of the introduction of adalimumab biosimilars was

found to be associated with highest savings compared to Flixabi® and Erelzi® entry (Table 4). The net budget impact of the entry of these new biosimilars was two times higher in RD compared to IBD (Table 4).

Table 4 Budget impact of adoption of new biosimilars in rheumatology and gastroenterology specialities in UK in British pounds sterling

		Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Total
Reference case (no new biosimilars entry)	RD	-30,987,173	-20,489,593	3,116,088	-48,360,678
	IBD	-6,573,865	2,202,941	8,730,433	4,359,509
Infliximab biosimilar (Flixabi®) entry	RD	-380,046	-694,037	-1,053,356	-2,127,439
	IBD	-1,287,986	-1,825,976	-3,007,921	-6,121,883
Etanercept biosimilar (Erelzi®) entry	RD	-671,772	-1,515,143	-6,309,710	-8,496,625
	IBD	-	-	-	-
Adalimumab biosimilars (Solymbic®, Amgevita® and Imraldi®) entry	RD	-25,396,052	-59,854,051	-91,623,114	-176,873,217
	IBD	-14,219,076	-31,449,623	-45,499,677	-91,168,376
All new biosimilars entry (Flixabi®, Erelzi®, Solymbic®, Amgevita® and Imraldi®)	RD	-26,447,870	-62,063,232	-98,986,181	-187,497,283
	IBD	-15,507,063	-33,275,599	-48,507,599	-97,290,261

3.3. Sensitivity analysis

The results of sensitivity analysis for all biosimilars entry in RD are shown in Figure 3. The highest total impact on savings was calculated by changing biosimilars market uptake.

4. Discussion

Our BIA estimated the impact of the introduction of new biosimilars in RD and IBD on the NHS healthcare budget in the UK. Our study is the first calculating savings realised from the introduction of adalimumab biosimilars in rheumatology and gastroenterology specialities in the UK. This BIA model was based on the previous UK market behaviour as a result of the introduction of infliximab and etanercept biosimilars (Inflectra®, Remsima® and Benepali®) from retrospective data (DEFINE Software), data from the medicine optimisation dashboard about infliximab and etanercept biosimilars uptake in UK acute Trusts, and the results from HCPs interviews. The results of this analysis showed that the introduction of new infliximab, etanercept and adalimumab biosimilars will deliver a considerable cost saving to the NHS (Table 4). These savings are in line with the NHS aims and vision that introduction of biosimilars has the potential to realise savings of at least £200-300 million per year by 2020/21 [37].

According to NICE guidelines, with the availability of more than one suitable treatment option, the less expensive agent including biosimilars should be chosen [5]. Infliximab and etanercept biosimilars have been considered as first-line agents in IBD and RD; respectively by some regional/local medicines management group/local formularies [38, 39]. The relatively rapid penetration of infliximab and etanercept biosimilars in IBD and RD market; respectively, (Figures 1 and 2) indicates that these products are prescribed for stabilised and biological naïve patients. This inference is further supported by the British Society of Gastroenterology statement (in 2016) which supported both initiation and switching to infliximab biosimilars and early data from the British Society for Rheumatology biologics register for RA (in 2017) that RD patients are actively being switched to infliximab and etanercept biosimilars for cost reasons [40, 41].

An unexpected market response to the entry of biosimilars was seen during 2015-2016, when the market share of infliximab and etanercept (reference biological product and biosimilars) decreased following the introduction of their corresponding biosimilars (Figures 1 and 2). In contrast, the market share of biologics not subjected to biosimilars competition such as golimumab, certolizumab, tocilizumab, abatacept and vedolizumab increased (Figure 1). This may be due to treatment failure, inadequate response, inability to tolerate, contraindication or adverse effect with other biologics and require switching to another molecule. For example, 5% of IBD patients cannot tolerate treatment with infliximab or adalimumab, and these biologics were ineffective in 41% of CD

patients [28]. Similarly, 5.9% of RA patients have a contraindication or cannot tolerate anti-TNFs such as infliximab and adalimumab [42]. Moreover, some physicians' reluctance and/or concerns to prescribe biosimilars may also influence their choice of treatment from molecules with biosimilars to agents not subjected to biosimilars competition [43]. Switching among bDMARDs/bDMAIDs depends on the clinician's decision to a second agent or an agent with a different mechanism of action [44]. Therefore, it would be expected that with the entry of more biosimilars (Flixabi® and Erelzi®) at the beginning of 2018 and adalimumab biosimilars late at the end of 2018, the market share of adalimumab (reference biological product and biosimilars) would also decrease following the introduction of adalimumab biosimilars. The increased market share of agents not subjected to biosimilars competition, i.e. reference biological agents which are more expensive, as well as population growth, was responsible for the increased expenditure in the IBD reference case scenario and offsetting of savings from existing and new biosimilars in all other scenarios (Table 4) This factor was not taken into account in other BIAs.

The Flixabi® entry model (Table 4) was associated with the least savings compared to the other models despite the 50% discounted price compared to other infliximab biosimilars. This may be due to the fact that the infliximab market has been subjected to two established biosimilars and the majority of patients that were on Remicade® have already been switched to Remsima® and Inflectra®. This is supported by data from the Medicines Optimisation Dashboard that indicated that infliximab biosimilars utilisation ranged 0-49% in 14 Trusts, 50-89% in 54 Trusts and 90-100% in 42 Trusts in April 2017 out of a total of 110 Trusts using infliximab in all specialities [35]. Therefore, it is likely that only a small proportion of patient on Remicade® would be eligible to be switched to Flixabi® and/or Flixabi® would be reserved for newly diagnosed patients. The Flixabi® model included a price reduction of existing infliximab biosimilars in response to increased competition. The impact of this scenario was higher in IBD than in RD since the proportion of patients treated with infliximab were much higher in IBD than those in RD.

Etanercept is not licenced for use in IBD, therefore the results of the Erelzi® entry model was limited to RD. In this model, Erelzi® was assumed to be introduced at a 10% lower price than the currently available etanercept biosimilar (Benepali®). The budget impact of Erelzi® introduction was higher than that of Flixabi® since the utilisation of etanercept is much greater than infliximab in the RD market. The time of Erelzi® entry is critical in the analysis, since Benepali® was launched in 2016 and patients switching plans from Enbrel® to Benepali® was only started in 2017 (based on HCPs opinions). The medicines optimisation dashboard data indicated that etanercept biosimilars utilisation ranged 0-49% in 43 Trusts, 50-89% in 37 Trusts and 90-100% in 24 Trusts in April 2017 out of a total of 104 Trusts using etanercept in all specialities [35]. This means unlike infliximab, there is more opportunity for competition between Benepali® and Erelzi® to be used in newly diagnosed patients and for switching existing patients on Enbrel®. We modelled that this greater competition in the etanercept market would lead to more price reductions which would affect the price of Enbrel®; the model suggests a fall of 50% to remain competitive.

The adalimumab biosimilars entry model was based on a mixture of the experience following the entry of the etanercept and infliximab biosimilars. Due to the similarity between etanercept and adalimumab in terms of being the market dominants in the RD market, having a similar market share, mode of administration in patient-friendly devices and similar price per defined daily dose (before the entry of biosimilars), the entry price of these new biosimilars was modelled on that of Benepali®. As it is expected that the three adalimumab biosimilars will be introduced at the same time, this is likely to provoke competition between these biosimilars (themselves) and with the brand (Humira®) in a similar way to how the market reacted when Inflectra® and Remsima® were launched at the same time in March 2015. Therefore, the subsequent price reductions seen in the infliximab market was used to model the price changes following the introduction of the three adalimumab biosimilars. Moreover, previous prescribers' experience with infliximab and etanercept biosimilars would be reflected in easier (smoother) and faster entry into adalimumab market than the entry of infliximab and etanercept biosimilars.

Despite the differences between biosimilars and generic medicines in term of structure, development and authorisation, generic and biosimilars share the similar commercial concepts of being a less expensive copy,

marketed following the patent expiry of the reference medicine [45]. The rapid and dramatic entry of infliximab and etanercept biosimilars was similar to some extent the entry of generic medicines. Infliximab biosimilars dominated the infliximab market in RD and IBD specialities in 3 years and in our BIA, is expected to replace Remicade® completely in the next 1-2 years (Figures 1 and 2). The same situation could be applied for etanercept and adalimumab biosimilars. This utilisation trend and the market penetration of these biosimilars is similar to the entry of generic medicines in the statins market [46].

Several BIAs assessing the impact of the introduction of infliximab and etanercept biosimilars were found in the literature [17-25]. As these BIAs were conducted in different countries in Europe, the total spending on bDMARDs and bDMAIDs varies between countries and the comparisons between international budgets would be inappropriate. A study by Ruff et al., (2015) estimated the five-year budget impact of etanercept biosimilars in the UK would result in savings of £100-£260 million based on the assumption that the etanercept biosimilar (Benepali®) price would be between 10-25% lower than that of Enbrel® [23]. Although our BIA was based on three-year time horizon, a lower total figure was anticipated to be achieved (from our previous analysis which showed that Benepali® achieved £23.4 million in the first year [16]. The results of this analysis in the reference case showed savings of £48 million mainly from (Benepali®), since RD are higher users of etanercept than IBD, and anticipated savings from Erelzi® entry (Table 4). The Ruff et al., study, did not take into account the impact of the competition between the Enbrel® and Benepali®, nor the entry of further biosimilars that would stimulate more competition with further price reductions and subsequent savings.

Kanters et al., study estimated the adoption of infliximab biosimilars over five years in RD and IBD in UK, Germany, France, Spain and Italy based on 2012/13 data. A relatively low number of clinicians from each of the five European countries participated in this Delphi survey [25]. For compatibility reasons, we compared our results with the UK results of this study. Kanters et al., forecasted that the UK uptake of all infliximab biosimilars would gradually increase from 0% at the beginning of the analyses (year 0) to 2.5% by year 5 in RD and 12.5% in IBD; prices were fixed during the study period for both reference and biosimilar infliximab. Biosimilar infliximab was set at 50% discount of Remicade® list price with expected savings from the entry of infliximab biosimilars in UK of £181 million in RD and £770 million in IBD over five years.

Our results showed less savings were associated with the entry of infliximab biosimilars (£48 million from already in use biosimilars with further £2 million from the entry of the third biosimilar (Flixabi) in RD. This discrepancy between Kanters et al., study and our results could be attributed to a number of factors. Kanters et al., used market shares at 2012/13 that did not reflect the dynamic changes in the RD and IBD markets following the entry of Inflectra® and Remsima®. Furthermore, the prices used in Kanters et al., model were the list prices, which were fixed during the study period, the biosimilar price discount was overestimated at 50%, and did not take into account the competition between the brand and the biosimilars and subsequent price reductions. In contrast our model was based on real-life utilisation and price data reflecting market behaviour. Furthermore, the Kanters et al., study was based on Delphi survey results in 2015, when infliximab biosimilars had just been launched in the UK market and HCPs had a no or little experience with bDMARDs and bDMAIDs biosimilars. The Kanters et al., study also overestimated vedolizumab market share and suggested an abrupt entry of this molecule into the IBD market. Our study based on actual utilisation data showed that vedolizumab entry was gradual since its availability in 2014 (Figure 2).

Severs et al., (2017) estimated the impact of the introduction of biosimilars in IBD (2015-2019) in Netherlands [47]. This BIA was based on Dutch data (prevalence and cost). Although this BIA expected a price reduction of Remicade® in response to biosimilars competition, they also expected a price reduction of reference adalimumab (Humira®) in response to the entry of infliximab biosimilars and potential switching from adalimumab to infliximab biosimilars. Furthermore, this BIA did not estimate the entry of adalimumab biosimilars or the entry of vedolizumab and golimumab, which our real-world data has shown to have a substantial impact on the IBD market.

The strengths of this study are that it is the first to calculate the impact of the entry of adalimumab and new infliximab and etanercept biosimilars. Furthermore, the assumptions in the BIA models were based on retrospective real-life utilisation and prices data. As with all BIAs, our model had limitations. Whilst rituximab

is an option in the treatment of RD when other biologics have failed, there is no defined daily dose index for this molecule due to its highly-individualised utilisation and wide dosage ranges. Therefore, rituximab utilisation cannot be compared to other bDMARDs and has not been included in this BIA. The recent introduction of three rituximab biosimilars in 2017 in UK, will undoubtedly produce additional cost savings. The model assumptions were based on previous market performance and HCPs perspectives. With the plethora of biosimilars entering the marketing and experience with biosimilars increasing the market dynamics may change over the period of the BIA. Administration and therapy monitoring costs were not included (assumed to be the same) since no switching between different molecules was anticipated. Although we acknowledged that there may be hidden administrative cost associated with switching and registering patients on disease registries as recommended by the National Rheumatoid Arthritis Society [48].

5. Conclusion

According to this BIA, the introduction of new infliximab, etanercept and adalimumab biosimilars will be associated with considerable cost savings and have a substantial favourable impact on the UK NHS budget. The number of biosimilars and time of entry of is critical to create competition that leads to more cost savings. Despite the potential increase in the number of biosimilars, the use of reference bDMARDs/bDMAIDs not subjected to biosimilars competition is likely to continue to increase and offset some of the savings produced by biosimilars.

References

1. Barber S, Sutherland N. National Arthritis Week 2016. 2016. http://researchbriefings.files.parliament.uk/documents/CDP-2016-0182/CDP-2016-0182.pdf. Accessed 12 Oct 2017.
2. The British Gastroenterology Association. Chronic management: Inflammatory Bowel Disease. 2017. http://www.bsg.org.uk/clinical/commissioning-report/chronic-inflammatory-bowel-disease.html. Accessed 12 Oct 2017.
3. National Institute for Health and Care Excellence. Rheumatoid arthritis in adults: management. 2015. https://www.nice.org.uk/guidance/cg79/resources/rheumatoid-arthritis-in-adults-management-pdf-975636823525. Accessed 12 Oct 2017.
4. Harrogate and District NHS Foundation Trust. Specialist Inflammatory Bowel Disease service created. 2017. https://www.hdft.nhs.uk/news/ibdservice/. Accessed 13 Oct 2017.
5. National Institute for Health and Care Excellence. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. 2016. https://www.nice.org.uk/guidance/ta375/resources/adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-tocilizumab-and-abatacept-for-rheumatoid-arthritis-not-previously-treated-with-dmards-or-after-conventional-dmards-only-have-failed-pdf-82602790920133. Accessed 12 Oct 2017.
6. National Institute for Health and Care Excellence. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. 2015. https://www.nice.org.uk/guidance/ta329/resources/infliximab-adalimumab-and-golimumab-for-treating-moderately-to-severely-active-ulcerative-colitis-after-the-failure-of-conventional-therapy-pdf-82602495307717. Accessed 12 Oct 2017.
7. Louis E, Mary JY, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology. 2012;142(1):63-70.e5. https://doi.org/10.1053/j.gastro.2011.09.034.
8. van der Valk ME, Mangen M-JJ, Severs M, et al. Evolution of costs of inflammatory bowel disease over two years of follow-up. PLoS One. 2016;11(4):e0142481. https://doi.org/10.1371/journal.pone.0142481.
9. Gulácsi, L., Brodszky, V., Baji, P., et al. Biosimilars for the management of rheumatoid arthritis: economic considerations. Expert Rev Clin Immunol. 2015;11(sup1):43-52. https://doi.org/10.1586/1744666X.2015.1090313.
10. European Medicines Agency. European public assessment reports. 2017. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&keyword=Enter%20keywords&searchType=name&alreadyLoaded=true&status=Authorised&jsenabled=false&searchGenericType=biosimilars&orderBy=authDate&pageNo=1. Accessed 13 Oct 2017.
11. Eversheds Sutherland. Clearing the path for biosimilar Humira™/adalimumab market entry in the UK – the English Patents Court considers how its small molecule case law applies to the world's highest selling biologic. 2016. http://www.eversheds-sutherland.com/global/en/what/articles/index.page?ArticleID=en/Healthcare/Clearing-biosimilar-Humira®-adalimumab-market-entry-UK. Accessed 13 Oct 2017.
12. Chapman SR, Fitzpatrick RW, Aladul MI. Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: result of a UK web-based survey. BMJ Open. 2017;7:e016730. https://doi.org/10.1136/bmjopen-2017-016730.
13. Health Information and Quality Authority. Guidelines for the Budget Impact Analysis of Health Technologies in Ireland. 2014. https://www.hiqa.ie/system/files/Budget-Impact-Analysis-Guidelines-2014.pdf. Accessed 13 Oct 2017.
14. Mauskopf J, Earnshaw SR, Brogan A, Wolowacz S, Brodtkorb TH. Budget-Impact Analysis of Health Care Interventions: A Practical Guide. Gewerbestrasse, Switzerland: Springer. 2017. p 103-126. https://doi.org/10.1007/978-3-319-50482-7_7.

15. Orlewska E, Gulácsi L. Budget-impact analyses. Pharmacoeconomics. 2009;27(10):807-827. https://doi.org/10.2165/11313770-000000000-00000.
16. Aladul MI, Fitzpatrick R, Chapman SR. Impact of infliximab and etanercept biosimilars on biological disease modifying antirheumatic drugs utilisation and NHS budget in UK. BioDrugs. 2017;31(6):533-544. https://doi.org/10.1007/s40259-017-0252-3.
17. Jha A, Upton A, Dunlop WC, Akehurst R. The budget impact of biosimilar infliximab (Remsima®) for the treatment of autoimmune diseases in five European countries. Adv Ther. 2015;32(8):742-756. https://doi.org/10.1007/s12325-015-0233-1.
18. McCarthy G, Bitoun CE, Guy H. Introduction of an infliximab biosimilar (CT-P13): a five-year budget impact analysis for the treatment of rheumatoid arthritis in Ireland [Abstract]. Value Health. 2013;16(7):A558. https://doi.org/10.1016/j.jval.2013.08.1465.
19. Brodszky V, Baji P, Balogh O, Péntek M. Budget impact analysis of biosimilar infliximab (CT-P13) for the treatment of rheumatoid arthritis in six Central and Eastern European countries. Eur J Health Econ. 2014;15(1):S65-71. https://doi.org/10.1007/s10198-014-0595-3.
20. Kim J, Hong J, Kudrin A. 5 Year budget impact analysis of biosimilar infliximab for the treatment of rheumatoid arthritis in UK, Italy, France and Germany [Abstract]. Arthritis Rheumatol. 2014;11(1):S512.
21. Lucioni C, Mazzi S, Caporali R. Budget impact analysis of infliximab biosimilar: the Italian scenery. Glob Reg Health Technol Assess. 2015;2:78-88. https://doi.org/10.5301/GRHTA.5000194.
22. Beck M, Michel B, Rybarczyk-Vigouret MC, Sordet C, Sibilia J, Velten M. Biosimilar infliximab for the management of rheumatoid arthritis in France: what are the expected savings?. Eur J Hosp Pharm. 2017;24:85-90. https://doi.org/10.1136/ejhpharm-2016-000904.
23. Ruff L, Rezk MF, Uhlig T, Gommers JW. Budget impact analysis of an etanercept biosimilar for the treatment of rheumatoid arthritis in Europe [Abstract]. Value Health. 2015;18(7):A639. https://doi.org/10.1016/j.jval.2015.09.2276.
24. Trancart M, Lafuma A, Laurendeau C. Budget Impact of Etanercept Biosimilars In the Treatment of Rheumatoid Arthrisis: An Analysis Based on French National Claims Database [Abstract]. Value Health. 2016;19(7):A532-A533. https://doi.org/10.1016/j.jval.2016.09.1082.
25. Kanters TA, Stevanovic J, Huys I, Vulto AG, Simoens S. 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. https://doi.org/10.3389/fphar.2017.00322.
26. Rx Info. Define. 2017. https://www.rx-info.co.uk/products/define/. Accessed 5 Oct 2017.
27. National Institute for Health and Care Excellence. Costing statement: Ulcerative colitis. Implementing the NICE guidance on infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (TA329). 2015. https://www.nice.org.uk/guidance/ta329/resources/costing-statement-pdf-428356477. Accessed 3 Oct 2017.
28. National Institute for Health and Care Excellence. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. 2015. https://www.nice.org.uk/guidance/ta352/resources/vedolizumab-for-treating-moderately-to-severely-active-crohns-disease-after-prior-therapy-pdf-82602664948933. Accessed 3 Oct 2017.
29. National Institute for Health and Care Excellence. Tocilizumab for the treatment of rheumatoid arthritis (review of NICE technology appraisal guidance 198). 2012. https://www.nice.org.uk/guidance/ta247/resources/costing-statement-pdf-423692173. Accessed 3 Oct 2017.
30. Humphreys JH, Verstappen SM, Hyrich KL, Chipping JR, Marshall T, Symmons DP. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Ann Rheum Dis. 2013;72(8):1315-1320. https://doi.org/10.1136/annrheumdis-2012-201960.
31. National Institute for Health and Care Excellence. TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. 2016.

https://www.nice.org.uk/guidance/ta383/resources/tnfalpha-inhibitors-for-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-pdf-82602848027077. Accessed 3 Oct 2017.

32. Hamilton L, Gilbert A, Skerrett J, Dickinson S, Gaffney K. Services for people with ankylosing spondylitis in the UK—a survey of rheumatologists and patients. Rheumatology. 2011;50(11):1991-1998. https://doi.org/10.1093/rheumatology/ker013.
33. National Institute for Health and Care Excellence. Costing statement: Golimumab for the treatment of psoriatic arthritis. 2011. https://www.nice.org.uk/guidance/ta220/resources/ta220-psoriatic-arthritis-golimumab-costing-statement2. Accessed 3 Oct 2017.
34. Office for national statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland. 2017. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland. Accessed 2 Oct 2017.
35. National Institute for Health and Care Excellence. Medicine Optimisation Dashboard. 2017. https://apps.nhsbsa.nhs.uk/MOD/AtlasTrustsMedsOp/atlas.html. Accessed 10 Oct 2017.
36. The Centre for Biosimilars. UK Authority: Merck Used Illegal Discounts to Defend Against Biosimilar Competition to Remicade. 2017. http://www.centerforbiosimilars.com/news/uk-authority-alleges-merck-used-illegal-discounts-to-defend-against-biosimilar-competition-to-remicade. Accessed 23 Oct 2017.
37. NHS England. Commissioning framework for biological medicines (including biosimilar medicines). 2017. https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf. Accessed 23 Oct 2017.
38. Greater Manchester Medicine Management Group. Biologics Pathways for Inflammatory Bowel Disease in Adults. http://gmmmg.nhs.uk/docs/consultation/Biologics-pathway-for-Inflammatory-Bowel-Disease-in-Adults-v1-2.pdf. Accessed 23 Oct 2017.
39. Greater Manchester Medicine Management Group. Etanercept biosimilar (Benepali®▼) for the treatment of the following diseases: Rheumatoid arthritis (RA), Axial spondylitis (AS), Psoriatic arthritis and Plaque psoriasis. 2016. http://gmmmg.nhs.uk/docs/nts/Benepali-etanercept-biosimilar-NTS-recommendation.pdf. Accessed 23 Oct 2017.
40. The British Society of Gastroenterology. BSG Guidance on the use of Biosimilar Infliximab CT-P13 in Inflammatory bowel disease (Online). 2016. http://www.bsg.org.uk/images/stories/docs/clinical/guidance/bsg_infliximab_guidance_16.Pdf. Accessed 24 Oct 2017.
41. De Cock D, Kearsley-Fleet L, Watson K, Hyrich KL. Switching from RA Originator to Biosimilar in Routine Clinical Care: Early Data from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis [abstract]. Arthritis Rheumatol. 2017;69(sup10). http://acrabstracts.org/abstract/switching-from-ra-originator-to-biosimilar-in-routine-clinical-care-early-data-from-the-british-society-for-rheumatology-biologics-register-for-rheumatoid-arthritis/ Accessed 24 Oct 2017.
42. National Institute for Health and Care Excellence. Tocilizumab for the treatment of rheumatoid arthritis (review of NICE technology appraisal guidance 198). 2012. https://www.nice.org.uk/guidance/ta247/resources/costing-statement-pdf-423692173 Accessed 24 Oct 2017.
43. Waller J, Sullivan E, Piercy J, Black CM, Kachroo S. Assessing physician and patient acceptance of infliximab biosimilars in rheumatoid arthritis, ankylosing spondyloarthritis and psoriatic arthritis across germany. Patient Prefer Adherence. 2017;11:519-530. https://doi.org/10.2147/PPA.S129333.
44. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014;73(3):492-509. https://doi.org/10.1136/annrheumdis-2013-204573.
45. mAbxience. Differences between biosimilars and generic drugs. 2017. http://www.mabxience.com/blogs/differences-between-biosimilars-and-generic-drugs/. Accessed 22 Oct 2017.

46. Chapman SR, Fitzpatrick RW, Aladul MI. Has cost inhibited the uptake of more potent statins in England? Pharmacoepidemiol Drug Saf. 2017;26:984-991. https://doi.org/10.1002/pds.4231
47. Severs M, Oldenburg B, van Bodegraven AA, Siersema, PD, Mangen, MJ. The economic impact of the introduction of biosimilars in inflammatory bowel disease. J Crohns Colitis. 2017;11(3):289-296. https://doi.org/10.1093/ecco-jcc/jjw153.
48. British Society for Rheumatology Position statement on biosimilar medicines (Revised January 2017). (2017). https://www.nras.org.uk/data/files/revised_bsr_biosimilars_position_statement_jan_2017.pdf

Figure 1 Retrospective and forecasted market shares of biologics between 2014 and 2020 in rheumatology specialities

Figure 2 Retrospective and forecasted market shares of biologics between 2014 and 2020 in gastroenterology specialities

Figure 3 One-way sensitivity results of ±10% of population, discount and biosimilars market uptake in RD