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ORIGINAL RESEARCH ARTICLE

A Look at the History of Biosimilar Adoption: Characteristics of Early and Late Adopters of Infliximab and Etanercept Biosimilars in Subregions of England, Scotland and Wales - A Mixed Methods Study

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Abstract

Background Regions within England, Scotland and Wales show variation in rate of adoption of biosimilar infliximab and etanercept.

Objectives This study aims to examine how local decisions and practices in regions within England, Scotland and Wales might explain initial variation in market dynamics of biosimilar and originator infliximab and etanercept.

Methods Market data provided by the National Health Service (NHS) on biosimilar and originator infliximab and etanercept uptake were analysed for the 10 historical regions of England, 14 health boards in Scotland and 7 health boards in Wales (2015–2018). Findings were discussed in ten semi-structured interviews: on a national level with an industry representative (1), on a regional level with NHS employees in England (6), Scotland (1) and Wales (1), and on a local level with a representative of a clinical commissioning group in England (1).

Results Tenders for infliximab and etanercept in England, Scotland and Wales have consistently resulted in a biosimilar as the best value biological. Early and late biosimilar adopters are seen, with overall convergence towards high biosimilar market shares over time. Qualitative results suggest that biosimilar adoption was positively influenced by (a) a price difference between biosimilar and originator product making it worthwhile to switch patients; (b) a good relationship between commissioner and provider in England resulting in gain share agreements; (c) leadership on biosimilars in regional NHS offices in England or Scottish and Welsh health boards; (d) key opinion leaders or leading hospitals that start using biosimilars early and gain experience.

Conclusions This study has shown that the savings potential drives biosimilar use. Regions with a proactive attitude, good stakeholder relationships, and clinician engagement were identified as early adopters.

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Key Points

Considerable variation in the rate of adoption of infliximab and etanercept biosimilars is observed within England, Scotland and Wales.

Implementation of biosimilars into clinical practice is facilitated by gain share agreements, regional and local leadership, and sharing of best practices from early adopters.

Over time, there is convergence towards high biosimilar market shares across England, Scotland and Wales.

1 Introduction

The loss of exclusivity of blockbuster tumour necrosis factor (TNF)-α inhibitors in 2015 (Remicade®: infliximab; Enbrel®: etanercept), and 2018 (Humira®: adalimumab) triggered the entry of biosimilars for these molecules into the European market. Biosimilar infliximab was the first biosimilar monoclonal antibody to receive a positive opinion from the European Medicines Agency (EMA), followed by marketing authorization for the European Union under the names Inflectra® and Remsima® [1]. Later, infliximab biosimilars Flixabi® and Zessly®, etanercept biosimilars Benepali® and Erelzi®, and adalimumab biosimilars Amgevita®, Imraldi®, Hyrimoz®/Hefiya®/Halimatoz®, Hulio®, Idacio® and Amsparity® were authorized. A full list of authorized biosimilars and marketing authorization dates can be consulted on the website of the EMA [1].

As spending on infliximab, etanercept and adalimumab for the National Health Service (NHS) in England totalled £545 million of the £16.8 billion that was spent on medicines in the year 2015–2016 [2], competition from biosimilars could induce considerable savings. Uptake of biosimilars varies widely both across Europe [3] and within individual countries [4–9], due to variation in implemented pricing and reimbursement procedures and demand-side measures supporting the use of biosimilars [10]. A study by Alnahar et al. [6] indicated in 2017 that uptake of the first wave of biosimilars (i.e. somatropin, epoetin and filgrastim) varies geographically across Great Britain (England, Scotland and Wales), and warrants further investigation of the reasons for variability of biosimilar uptake. Two years after the entry of infliximab biosimilars in England, uptake still varied from below 10% biosimilar usage up to 99% across Acute Trusts (i.e. Hospital Trusts, accountable organisations within NHS England that manage and control the performance, services quality and financial efficiency of clusters of hospitals in England) [2]. Savings for infliximab and etanercept for the year 2017–2018 already totalled £166 million [11], but more could be achieved when fully leveraging biosimilar competition.

The aim of this study was to determine the influence of local decision making and practices on early biosimilar infliximab and etanercept adoption in subregions of England, Scotland and Wales. This builds further on our previous work investigating regional variation in uptake of biosimilar infliximab and etanercept in the 21 counties of Sweden [4, 5]. This similar study in Sweden has shown that the main driver for biosimilar use is the extent of the actual price difference, after discounts and rebates, between biosimilar and originator product. Additionally, the attitude of key opinion leaders, local guidelines and gain sharing influenced biosimilar/originator market dynamics. Enabling factors such as a multi-stakeholder approach, an altruistic attitude and good communication were also identified. In the present study on biosimilar adoption in subregions of England, Scotland and Wales, we want to validate these findings and study whether the drivers for biosimilar adoption in Sweden are also valid in other healthcare systems. In addition, approaches for the adoption of adalimumab biosimilars will be commented on in the discussion section of this paper, as a full analysis was not possible given their recent entry at the time of the study.

2 Methods

This study is a mixed methods study based on an exploratory literature review, a quantitative part including analysis of biosimilar uptake trends, and a qualitative part with semi-structured interviews.

An exploratory literature review was conducted in PubMed, combining search terms on biosimilars, the United Kingdom (UK), Great Britain, England, Scotland and Wales. In addition, a Google search was performed to include grey literature, such as websites and documents on biosimilars from the NHS in England, Scotland and Wales.

With a view to describing regional biosimilar uptake trends over time, biosimilar infliximab and etanercept market shares over time are presented for the ten historical subregions of England, fourteen health boards in Scotland and seven health boards in Wales (2015–2018). These market shares were calculated as volume of biosimilars over volume of biosimilars plus originator product, with volumes in defined daily doses (DDDs) in the case of England and Scotland, and in vials for Wales. As defined by the World Health Organization, a DDD of infliximab or etanercept is a unit that is expressed as the average daily maintenance dose for their main indication in adults, namely rheumatoid arthritis [12, 13]. Although the use of vials provides a more unambiguous view on the use of infliximab as only one strength is available (i.e. 100-mg vials), the calculation of a ratio to present market shares will render the same results when expressed in vials or DDDs. For etanercept, the use of DDDs is preferred to take into account different presentations. As the etanercept data for Wales are based on vials instead of DDDs, we would expect small discrepancies. Market data on biosimilar and originator infliximab and etanercept were provided by the NHS in England, Scotland and Wales through personal communication in the case of England and Wales, and via an information request for Scotland (HMUD and PRISMS databases [14]; please note that hospital drug utilisation does not necessarily equate to drug consumption). The ten-region level in England aligns with the former Strategic Health Authority areas as formed in 2006 after a reorganisation [15, 16], and was chosen since communication still occurs at this level (although abolished in 2013). In

Wales, changes were introduced in April 2019 with respect to the names and covered population of the health boards [17]. Names of the health boards used throughout the text and figures still reflect the situation before 1 April 2019. Early and late adopters are discussed by visually examining biosimilar uptake trends over time for the different regions. A more extensive (statistical) analysis was not possible given that the factors that seemed to influence biosimilar uptake are hard to quantify and the available data points (regions) are limited. Furthermore, we did not have access to actual prices, including discounts following tender procedures.

Ten semi-structured interviews (i.e. interviews that are conversational in tone, but guided by an interview guide [18]) were conducted in order to gain insight into which factors determined early and late adoption of biosimilars in the ten historical regions in England, fourteen health boards in Scotland and seven health boards in Wales. The focus of the study was initially on England, with its ten historical regions, and we later expanded to investigate whether the same drivers and enablers were found for Scotland and Wales. First, an overarching interview was conducted with an industry representative to ask questions on the healthcare system in the UK, in addition to questions related to the biosimilars market. Then, six interviews were conducted with NHS England employees in NHS North East, NHS North West, NHS Yorkshire and the Humber, NHS East of England, NHS West Midlands, and NHS South East Coast. Via these six interviews, information was also obtained on the four remaining regions (East Midlands, London, South West and South Central) for which no specific interview was carried out. One interview with a representative of a clinical commissioning group (an organisation that pays for healthcare services and medicines) in England was conducted to explore whether the obtained information on a regional level corresponds with factors that are perceived to influence biosimilar adoption on a local level. Finally, in order to broaden the scope of the study, two interviews were conducted with representatives from NHS Scotland and NHS Wales.

Interviewees were contacted via email for their participation. Once confirmed, an informed consent form was shared to ask for permission to record the interview for transcription purposes. The interviews were conducted via telephone, based on an interview guide to structure the interview, and were later transcribed *verbatim*, pseudonymised and analysed in a qualitative way. A framework approach, which is often adopted in applied qualitative research, was used to analyse the data [19]. First the transcripts and notes taken during the interview were read to familiarize with the data, then a thematic framework was constructed based on topics in the interview guide (national, regional and local measures for different stakeholders) and issues emerging from the interviews; subsequently the framework was applied and the data were rearranged and interpreted [20]. Questions were related to policies and practices in a region, especially with regard to infliximab and etanercept biosimilars, and how they would explain regional variation and faster/slower biosimilar adoption in other regions. All interviews were carried out in English between September 2018 and February 2019. As the interviews served to gather information on policies and local practices, there might be overlap with results from the literature review. Furthermore, interviewees pointed out additional websites and documents, which are referred to where relevant.

Findings from this mixed methods study are reported in an integrated way, with references to the literature to corroborate interview results, and quantitative results further explained by learnings from the interviews. Some of our results might not be specific for just the biosimilar infliximab and etanercept market, since implemented policy measures might have a broader scope. In addition, some barriers and facilitators for biosimilar adoption might not be product specific. However, this can only improve the generalizability of the study results to other biosimilar products.

3 Results

Integrated results of the literature review, data analysis and interviews are discussed separately for England, Scotland and Wales. However, we observed some common characteristics for these countries with regards to the infliximab and etanercept market, that is, both molecules are procured by tendering and prescribed by brand name by specialists in the hospital, infliximab is administered in the hospital and etanercept mainly via homecare services, biosimilars for infliximab and etanercept have been the best value offer in tender procedures in England, Scotland and Wales. It was reported during the interviews that clinicians' confidence is growing with hands-on experience and more evidence about the efficacy and safety of biosimilars and switching from the originator to the biosimilar. In addition, pharmacists and other healthcare professionals, such as nurses, support the switch process. When correctly framed and considering shared decision making, patients have also accepted a switch to a biosimilar. A major difference between the healthcare system in England versus Scotland and Wales is the commissioner-provider split in England, where you have clinical commissioning groups (CCGs) on the demand side and hospital trusts on the supply side [21]. In addition, tender prices can differ between regions in England, while there is only one national price in Scotland and Wales [2].

3.1 England

3.1.1 General Observations of the Biosimilars Market

In England, the provision of healthcare and integration of national policy measures on a local level is governed by the different CCGs and Trusts, with overarching regional structures to align implementation, such as the former ten Strategic Health Authorities at which level communication related to biosimilars still occurs. In addition to the work of the CCGs, specialised care such as medicines for the treatment of cancer is commissioned by NHS England itself. This is the case for originator and biosimilar trastuzumab, and for the oncology indications for originator and biosimilar rituximab, while this is the responsibility of the CCGs for infliximab and etanercept.

Several national position statements and recommendations on the use of biosimilars are in place. A non-exhaustive overview is provided in Table 1. In general, the biosimilar market in England is characterized by a high focus on education and open discussion; for example, via national initiatives as outlined in Table 1, regional workshops, and documents on the website of the NHS Specialist Pharmacy Service, including a toolkit for the adoption of biosimilar adalimumab [22]. In addition, uptake of biosimilars is closely monitored and matched with appropriate activities to improve their use.

Competitive pricing for infliximab and etanercept occurs via a special tender procedure. First, a national tender is set up resulting in a framework agreement with usually a number of manufacturers in order to determine prices on a national level. Then, a 2-year rotational tendering system starts in the four regions (London, North, South, and Midlands and East of England), with a new tender starting in a different region every 6 months. This gives the opportunity for companies to compete in multiple tenders and still provides a large volume to the winner. However, even though tendering occurs on a four-region level, decisions still tend to be taken on a ten-region level as this facilitates communication.

3.1.2 Regional Approaches Towards the Entry of Infliximab and Etanercept Biosimilars

3.1.2.1 Infliximab Although all regions should follow national policy, differences exist in how well this is imple-

Table 1 A non-exhaustive overview of policy measures and recommendations related to biosimilars in England

Year	Details
2015 and 2019	In September 2015, NHS England published an information guide ('What is a biosimilar medicine?') with the aim to educate stakeholders on the role of biosimilars [51]. This guide was created in collaboration with industry and pharmacists' associations, and regulatory and health technology assessment (HTA) authorities. An update was published in May 2019, also involving a patient organisation for rheumatoid arthritis patients and clinicians (via the Biosimilars Programme Board) [52].
2015–2018	The National Institute for Health and Care Excellence (NICE), England's HTA body, had updated already in 2015 its guidelines for evaluation of biosimilars [53]. In addition, from 2016 to 2018, NICE provided updates on the information and evidence available for adoption of biosimilars within NHS England [54], and has published specific medicines evidence commentaries on, for example, bioequivalence between biosimilar and reference TNF-α inhibitors in 2017 [55].
2017	In September 2017, NHS England published its Commissioning framework for biological medicines (including biosimilars medicines), which urges commissioners to leverage competition from biosimilars via a collaborative approach and sets out a target of at least 90% of new patients on the best value biological medicine within 3 months after the entry of a biosimilar [2]. When choosing a best value biological medicine, which can be either the biosimilar or the originator depending on the offer, an evaluation needs to be carried out of "*transparently costed device training, any patient support programs offered by manufacturers, administration costs, dosage and price per dose*" [2]. Furthermore, at least 80% of existing patients should be switched to the best value biological product within 12 months after the entry of the biosimilar. When this target is not reached, commissioners will have to provide justification. For hospitals, these targets are linked to a financial incentive through a Commissioning for Quality and Innovation (CQUIN) scheme [56].
2017	To ensure local implementation, biosimilars have been taken up by the Regional Medicines Optimisation Committees (RMOCs). Four RMOCs that cover London, the South, the North, and the Midlands and East of England started in 2017 targeted with reducing variation in the optimal use of medicines between regions and aligning local implementation of national policy measures [57]. Regional procurement pharmacists try to align national and regional policy and facilitate implementation by, for example, highlighting to trusts what the potential savings are and producing reports to demonstrate this.
2017	In 2017, the Cancer Vanguard, a part of the NHS established to follow up their National Cancer Strategy [58], developed in collaboration with Sandoz an interactive document with a proposed biosimilar adoption process timeline, including educational and supporting material for switching patients. The timeline flowchart initially aimed to facilitate the introduction of rituximab biosimilars in 2017, but is highly relevant for other therapeutic areas [59].
2018	In 2018, with the upcoming loss of exclusivity of originator adalimumab in mind, a national biosimilars programme board was created, consisting of hospital clinicians, pharmacists, procurement pharmacists, nurses, patient associations, authorities and industry (both biosimilar and originator), and is chaired by NHS England's Chief Pharmaceutical Officer. This board aims to drive biosimilar use by advising NHS England.

mented within each region. Figure 1 shows biosimilar infliximab market shares over time for the ten historical regions of England. Exclusivity rights on infliximab expired on February 24, 2015 in the UK, and first sales for infliximab biosimilars can be observed in March 2015. One year after the entry of biosimilar infliximab, market shares still varied from 15 to 83%. Two years later, this variation was reduced to 63–91%. However, it took up to August 2018, three and a half years later, for all regions to reach market shares of at least 90%. Quick and slow adopters can be observed in each of the four tender regions.

Upon visual examination, two early adopters can be clearly distinguished, NHS South Central (light orange line) and NHS South West (dark orange line), with two distinctive approaches to increase biosimilar infliximab market shares (clinician versus payer initiated, respectively). In the South Central region, Southampton General Hospital introduced a managed switching programme for inflammatory bowel disease (IBD) patients on infliximab in April 2015, led by Dr Fraser Cummings [23]. The existing good relationship between the hospital and local CCGs was used to arrange a 50:50 gain share agreement on cost savings, on top of agreed investments in staffing at the IBD department. Neighbouring hospitals in the South Central region also became early adopters. A second early adopter, the South West region, had one large CCG that introduced a capped medicines budget for hospitals, which forced the adoption of biosimilars in order not to exceed the budget. Trusts that were not in this CCG learned from the early experience with biosimilars of other hospitals and also became early adopters.

NHS Yorkshire and the Humber (red line) was initially a slow adopter of biosimilar infliximab, as they were concerned that the price of originator infliximab would go up when the volume decreased and did not want to take this risk, while other regions with the same procurement contract had a different interpretation. Once this was clarified, adoption of biosimilar infliximab quickly increased, aided by multi-stakeholder overarching regional committees that were proven effective in other clinical areas and focused on education of stakeholders, sharing of contract award information and follow up of uptake and local barriers. Collaboration between commissioners and providers led to gain share agreements for most trusts. A region that was lagging until 3 years after the entry of infliximab biosimilars is the West Midlands (dark green line), where this joined-up approach is lacking, and less interaction exists between CCGs and trusts. Also for other regions, negotiations on gain share agreements initially delayed uptake of biosimilar infliximab, with trusts without an agreement lacking resources to switch patients to the biosimilar. Some CCGs decided to initially only start new patients on the biosimilar to increase trust of clinicians in biosimilars, and in a later stage implement a switching process supported by financial resources.

3.1.2.2 Etanercept In Fig. 2, biosimilar etanercept market shares over time are presented for the ten historical regions in England. The first etanercept biosimilar received marketing authorization for use in the European Union in January 2016. First sales can be observed in March 2016 but are limited to one region (1% in the South West region). One year later, biosimilar etanercept market shares varied from 15 to 76%, and 2 years later from 54 to 87%. Visually examined, no distinctive early adopters can be identified for biosimilar etanercept. The South West, South Central and Yorkshire and the Humber regions are again quick adopters, along with the London region, while the West Midlands region lags behind again. Given the experience with biosimilar infliximab, the expectation would be that uptake of biosimilar etanercept is quicker. However, it was reported that the originator company tried to match the biosimilar price bid in the case of etanercept, resulting in a similar rate of uptake for biosimilar etanercept compared to biosimilar infliximab. A less clear financial benefit for the use of biosimilar etanercept slowed the switch to the biosimilar and made some regions, such as the West Midlands region, initially decide to stay with the originator product. In addition,

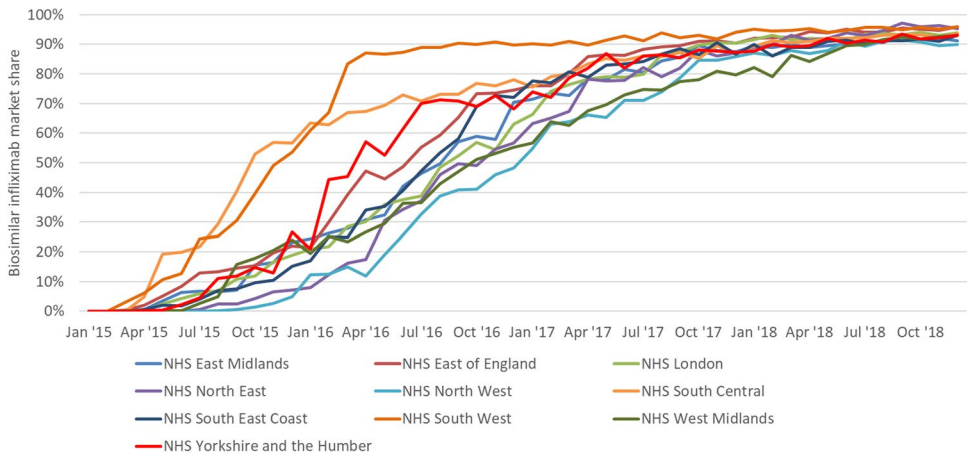

Fig. 1 Biosimilar infliximab market shares for the ten historical regions in England, calculated as volume (defined daily doses) of the biosimilars over volume of the biosimilars plus reference product, from 2015 to 2018

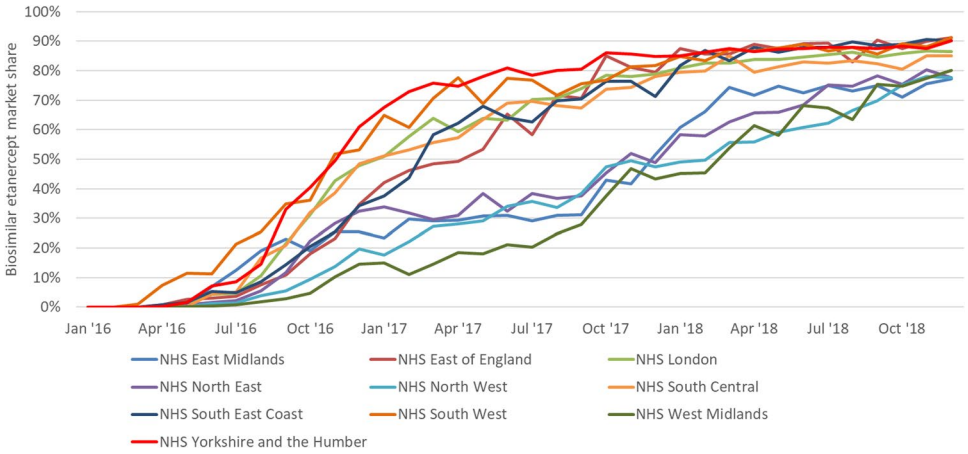

Fig. 2 Biosimilar etanercept market shares for the ten historical regions in England, calculated as volume (defined daily doses) of the biosimilars over volume of the biosimilars plus reference product, from 2016 to 2018

the training aspect for a different device is important and there is limited capacity available for this. Furthermore, it was mentioned that the homecare provision of etanercept offers patients more opportunity to discuss and potentially object to the switching process.

3.2 Scotland

In Scotland, there are 14 territorial health boards that are responsible for patient care in their area, covering both primary and secondary care services [24]. In addition to local decision making through the health boards, several national organisations exist that provide support and guidance on overall healthcare objectives, such as Healthcare Improvement Scotland, which developed a national prescribing framework for biosimilars in 2015, in consultation with the health boards [25]. In order to take into account advancing experience with biosimilars, this framework was updated in 2018 and provides more detailed information on clinical adoption of biosimilars, including good practice case studies and a patient switch letter template [26, 27]. Recommendations in this framework distinguish between new patients, who should be prescribed the most cost-effective biological, and existing patients, for whom a switch to a biosimilar should be considered when economically beneficial. The latter includes an assessment of the cost of change and the price difference between the originator and biosimilar product. The use of 'invest to save' arrangements (e.g. recruitment of additional staffing) is advised to help hospitals overcome the hurdle of switching patients. However, no formal gain share agreements exist with hospitals and all savings thus stay within the health board. Since the year 2018–2019, biosimilars are included as a secondary care National Therapeutic Indicator and uptake of biosimilar infliximab, etanercept and rituximab in the different health boards is published [28].

Given the national framework for tendering (unranked multi-supplier), the same prices apply throughout the country and do not contribute to regional variations. Implementation of policy measures and guidance for adherence to national policies is up to the 14 health boards, and this gives rise to considerable variation in uptake of biosimilar infliximab and etanercept (see Figs. 3 and 4). First sales for biosimilar infliximab can be observed only in April 2016 in Scotland. One year later, biosimilar infliximab market shares varied from 0 to 100%. When excluding smaller

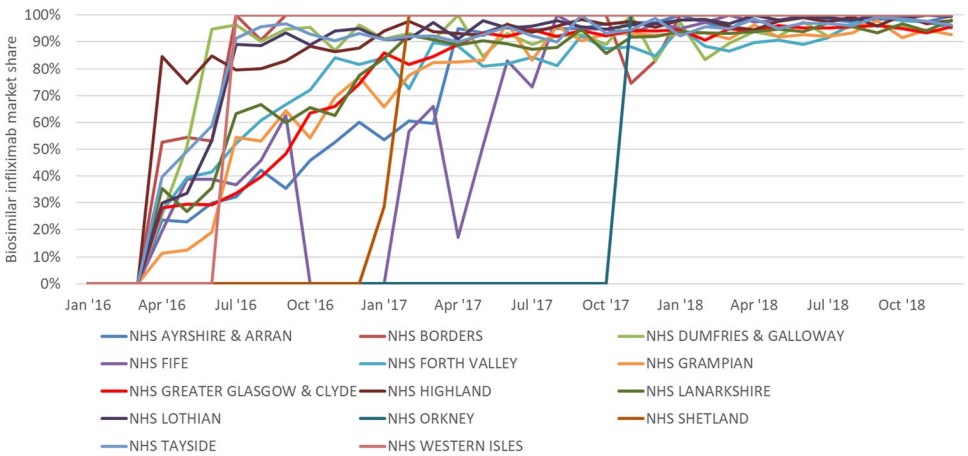

Fig. 3 Biosimilar infliximab market shares for the 14 health boards in Scotland, calculated as volume (defined daily doses) of the biosimilars over volume of the biosimilars plus reference product, from 2016 to 2018

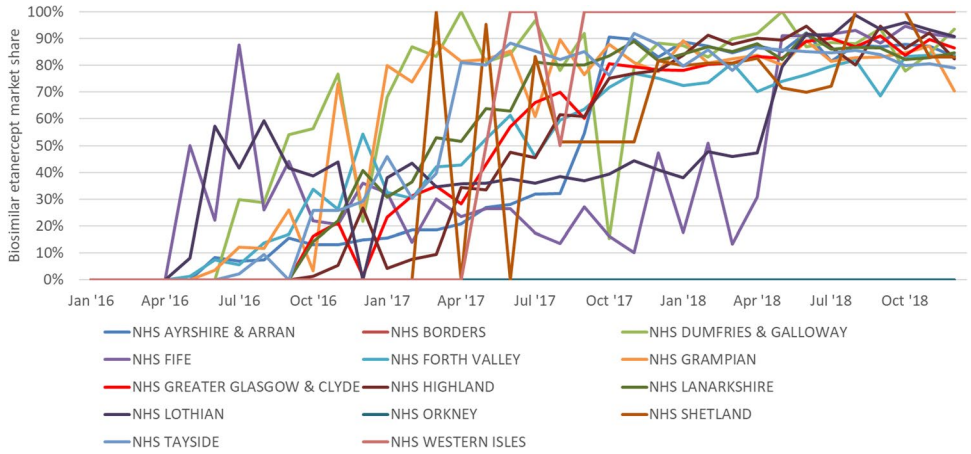

Fig. 4 Biosimilar etanercept market shares for the 14 health boards in Scotland, calculated as volume (defined daily doses) of the biosimilars over volume of the biosimilars plus reference product, from 2016 to 2018

health boards covering the islands of Scotland (Orkney, Shetland and Western Isles), this variation is reduced to 17–100%, with only one health board having biosimilar infliximab market shares below 80%. Two years after the entry of biosimilar infliximab, in April 2018, all health boards had biosimilar infliximab market shares between 90 and 100%. For biosimilar etanercept, first sales can be observed in May 2016, followed by large variations in uptake of biosimilar etanercept between the different health boards. At the end of 2018, this variation was limited to 79–94% (excluding regions with low use of etanercept, i.e. Borders, Orkney, Shetland and Western Isles). The slower uptake of biosimilar etanercept compared with biosimilar infliximab was attributed to a training aspect to make patients comfortable to use a new device for subcutaneous administration. This is further complicated by the use of homecare services for etanercept, versus a quick switch of an infusion of infliximab in the hospital setting.

Some health boards were quicker than others to adopt biosimilar infliximab and etanercept. At NHS Highland (dark brown line), the gastroenterology team decided to start IBD patients on biosimilar infliximab and switch existing patients from originator infliximab to a biosimilar as soon as the biosimilar became available (April 2016), in order to keep their budget under control [27]. They developed a switch letter to inform existing patients prior to their next appointment and offered the opportunity to discuss any questions they may have to make an informed decision. These switch letters were adopted on a national level in March 2016 for infliximab as well as etanercept and have been adapted by other health boards [26, 27]. Figure 3 shows that efforts from NHS Highland paid off, with a biosimilar infliximab market share of 85% in the first month. Many other health boards also made a quick start, with primarily smaller health boards lagging behind. Learnings from the gastroenterology team in NHS Highland were shared with the rheumatology team in order to successfully switch etanercept patients. However, as can be seen in Fig. 4, this took some time and compared with other health boards, they were late adopters. Results from a switch programme for rheumatology patients on etanercept in the NHS Grampian Health Board (orange line) that started in August 2016 [27] also experienced a lag of several months. Patients on etanercept normally have consultations scheduled only every 6 months. A mixed model was used to call back some patients earlier to make a switch to biosimilar etanercept.

Additional factors that were mentioned during the interview that might explain variation in biosimilar uptake between health boards were the presence of a project manager or clinical leader within the health board that drives the switch, and investments of some health boards in additional staffing to support the switch process. The latter was especially helpful for the switch to biosimilar etanercept, where additional consultations needed to be scheduled when proactively switching, and the change to a different device required training.

3.3 Wales

Within Wales, the seven autonomous health boards are responsible for health policies and guidance, for both primary and secondary care in their region. A national policy framework for biosimilars emphasises that biosimilars are a priority for NHS Wales and provides direction for all health boards. As of April 2016, prescribing of biosimilars has been an All Wales Medicines Strategy Group (AWMSG) National Prescribing Indicator (NPI). This indicator is to support cost-effective prescribing of selected biological medicines where biosimilar versions are available [29], therefore supporting the appropriate use of best value biologicals. Quarterly monitoring reports for NPIs, including on uptake of biosimilars versus their reference product, are published online by the Welsh Analytical Prescribing Support Unit (WAPSU), which is part of the All Wales Therapeutics and Toxicology Centre (AWTTC) [30]. These data show variation between the different health boards. In order to reduce variation and support

health boards to increase uptake of biosimilars, a variety of activities were undertaken. In 2017, biosimilars were part of a Best Practice Day, where experience in rheumatology from early adopter, Aneurin Bevan University Health Board, was shared with other health boards [31]. At the start of 2019, a dedicated multidisciplinary Biosimilar Best Practice Day was organised, with the aim to increase biosimilar uptake and reduce variation between health boards [32].

Challenges that have been raised concerning switching patients to the most cost-effective biosimilar are mainly related to a lack of capacity to have a conversation with existing patients on the reference product, leading to an initial delay in uptake of biosimilars. It is recommended that patients are involved in the decision making and give their consent before being switched to a biosimilar. Figures 5 and 6 show biosimilar infliximab and etanercept market shares for the individual health boards. First sales of biosimilar infliximab can be observed in quarter two of 2015. One year after the entry of biosimilar infliximab, market shares still varied from 12 to 83%, and after 2 years from 38 to 92%. At the end of 2018, this variation was reduced to 92–99%. First sales of biosimilar etanercept can be seen in quarter two of 2016, although only for one health board. One year after the entry of biosimilar etanercept, this variation still ranged from 0 to 81%. After 2 years, 54 to 98% and at the end of 2018, this variation was only 73–98%. For etanercept, three early and three late adopters can be clearly distinguished when examining Fig. 6.

The Aneurin Bevan University Health Board (dark blue line) can be clearly distinguished as an early adopter of both biosimilar infliximab and etanercept. In November 2015, a position statement on biosimilars was issued by the health board and signed by a rheumatologist who serves on the health board [33]. In June of 2017, this rheumatologist also shared experiences from the health board with biosimilars on the national Best Practice Day [31]. The Abertawe Bro Morgannwg University Health Board published its biosimilar strategy in January 2018, mentioning approved actions to increase biosimilar uptake from January 2017 [34].

During the interview, some additional factors were put forward that might explain differences in biosimilar uptake between health boards. Variation could be due to differences in the initial experience levels of clinicians attained from both in-practice, and wider factors such as conference attendance where information on the switching of biosimilars was presented.

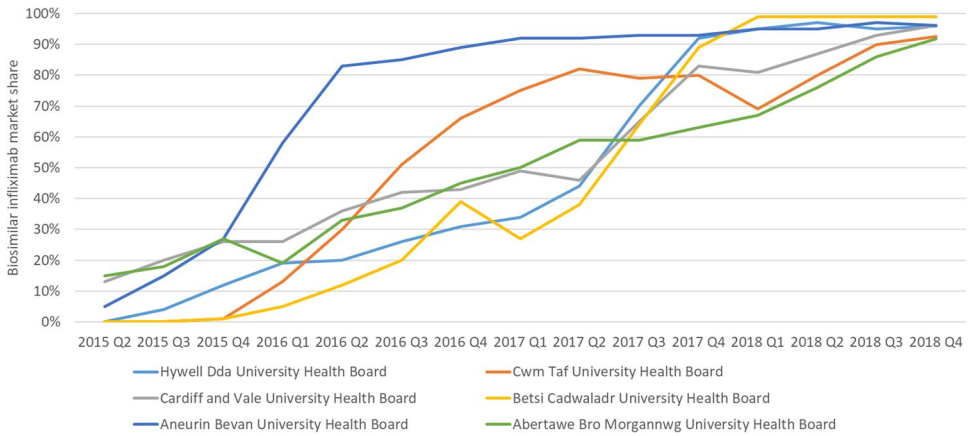

Fig. 5 Biosimilar infliximab market shares for the seven health boards in Wales, calculated as volume (vials) of the biosimilars over volume of the biosimilars plus reference product, from quarter two of 2015 to end of 2018. The seventh health board, Powys Teaching Health Board, is not shown, as this health board has no secondary care services

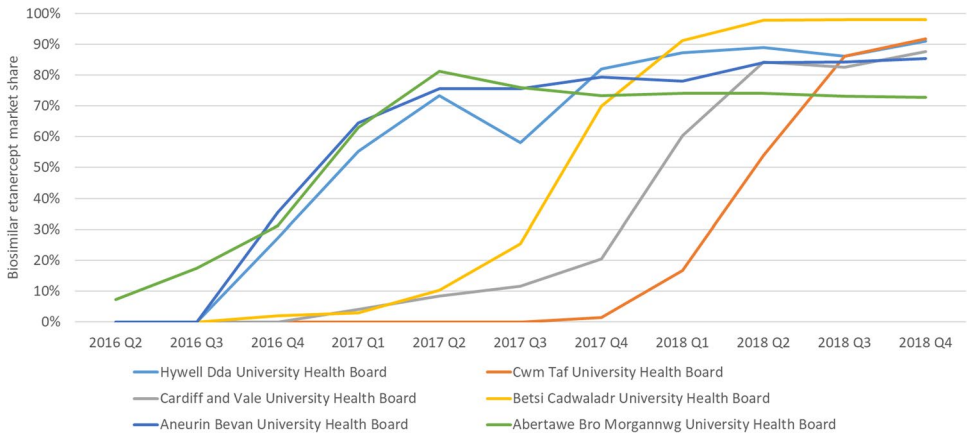

Fig. 6 Biosimilar etanercept market shares for the seven health boards in Wales, calculated as volume (vials) of the biosimilars over volume of the biosimilars plus reference product, from quarter two of 2016 to end of 2018. The seventh health board, Powys Teaching Health Board, is not shown, as this health board has no secondary care services

3.4 Factors Influencing Biosimilar Adoption

The identified factors that seem to positively influence biosimilar uptake in the studied regions are summarized in Table 2. The overall key driver for regions to adopt biosimilars are the cost savings that can be realized by moving to a lower-priced product. Although tendered prices might vary between the four regions in England (London, North, South, and Midlands and East of England) due to the regional rotation system, potential differences in regional prices do not seem to influence uptake. As hospitals acknowledged a lack of resources available to manage the switching process, the negotiation of a gain share agreement, where part of these savings is shared with the hospitals, led to considerable improvements in biosimilar uptake. Investments in additional staffing to support the switching process also resulted in higher rates of biosimilar adoption. These negotiations were facilitated by relying on existing good relationships and networks. In addition, leadership within the organisations in a region and forerunners at the hospital will enhance biosimilar uptake. Colleagues with experiences of biosimilar prescribing and switching of patients to a biosimilar are an important factor in changing prescribing behaviour of clinicians.

4 Discussion

The combination of a competitive pricing landscape where the biosimilar has been the least expensive treatment option and a strong focus on education and best practice sharing to eliminate initial scepticism and lack of understanding, have made the UK one of the European countries with the highest biosimilar market shares. This presents an interesting case study to illustrate how uptake has evolved over time and what drives biosimilar adoption. In this article, we describe regional-level decision making and practices related to the use of biosimilar infliximab and etanercept in the ten historical regions of England, 14 health boards in Scotland, and seven health boards in Wales, with a view to identify factors that characterize early and late adopters of these biosimilars and explain regional variation. This study adds to the scarce literature on factors influencing biosimilar adoption. Specifically for the UK, research has mainly focused on stakeholder perspectives on biosimilars and budget impact of biosimilars [35–41], while this article maps policies and local practices, and focusses on regional differences. A study by Alnahar et al. [6] already described geographical variability in uptake of biosimilars for somatropin, epoetin and filgrastim across Great Britain, but did not investigate local practices and factors influencing biosimilar adoption. Our findings align with results from a survey published in April 2018 from NHS England among CCGs and Trusts with the aim to identify barriers to biosimilar uptake and increase understanding of stakeholder positions [42, 43]. These reports highlight capacity problems to switch patients and a lack of clinician engagement as barriers to biosimilar adoption and found that gain share agreements and investment in additional staff are most often used as incentives to support a switch to a biosimilar.

Compared with results from our previous study on regional variation of biosimilar uptake in Sweden [4, 5], the lack of (staff) resources as a barrier to switch from the originator product to the biosimilar (and which needs to be overcome via specific gain share agreements) was less apparent in Sweden, where hospitals felt that they receive the budget they need and a more altruistic attitude prevailed to adopt biosimilars with a view to generate savings for the healthcare system. It should be noted that the biosimilar is not always less expensive than the originator product in Sweden, which complicates a comparison of regional variation and speed of biosimilar uptake between the UK and Sweden. However, in general, the identified drivers for biosimilar uptake also seem to be consistent among other European countries such as Germany and Belgium [44, 45]; that is, the initial driver depends on the size of the net price difference between the biosimilar and originator product, then further incentives are needed for physicians; for example, local guidelines, prescription targets and gain sharing. One should keep in mind that the ultimate goal is to introduce competition, leading to lowered treatment costs. In Sweden, a net price difference of 40% between originator and biosimilar infliximab led to high biosimilar market shares [4]. In the case of etanercept in Sweden, the importance of demand-side policies was highlighted, with high biosimilar market shares with only limited net price differences between originator and biosimilar [5]. Adoption of biosimilars is enabled by a proactive attitude with multi-stakeholder engagement, and a good relationship

Table 2 Identified factors in the qualitative analysis that positively influence regional-level uptake of biosimilar infliximab and etanercept in England, Wales and Scotland

Factors linked to high rate of biosimilar uptake (qualitative analysis)
A price differential between biosimilar and originator product (=potential cost savings)
Gain share agreements, aided by good relationships between commissioner and provider in England
Leadership on a regional/local level to implement national policy
Key opinion leaders in hospitals that gain early experience and motivate other clinicians

and communication between decision makers and other stakeholders. A paper by Khan et al. voiced the lack of information on the impact of relationships between different stakeholders on uptake of new medicines, and acknowledges a 'disconnect' between policy makers who want to increase biosimilar uptake, adopters who carry the burden of change, and available information on how to implement the use of biosimilars in practice [46]. However, relationships are not easy to change and definitely do not change quickly.

In general, regional variations and rate of uptake of biosimilar infliximab and etanercept by the regions seem to evolve in a similar way for England, Scotland and Wales. Uptake of biosimilar infliximab in Scotland can be observed to be quicker than in England and Wales, with most health boards having market shares above 80% after 1 year. However, it should be noted that the use of biosimilar infliximab in Scotland only started in April 2016, approximately 1 year later than in England and Wales. This probably influenced clinician engagement and preparedness to push a switch at the national and health board level. Furthermore, caution needs to be exercised when comparing biosimilar uptake patterns between England and Scotland/Wales because, for example, the regions are much larger in the former than in the latter. A higher uptake of biosimilar etanercept compared with biosimilar infliximab due to evolving experience with biosimilars is not as apparent as we would expect, as a result of smaller price differences between biosimilar and originator etanercept, and a difference in treatment setting (i.e. homecare services).

While this article has focused on uptake of biosimilar infliximab and etanercept, we noticed that the entry of biosimilars for the world's best-selling medicine, Humira® (adalimumab), at the end of 2018, has led to a revised strategy to ensure their adoption and to generate corresponding cost savings. For England, this meant that efforts were more nationally coordinated to avoid missing the opportunity for savings from the start. In 2016, a dedicated adalimumab web page was created by the Specialist Pharmacy Service with briefing documents from RMOC meetings, educational material, resources to facilitate practical implementation (such as patient letter templates, an Excel file with different steps of implementation, and a tool to track cost savings), clinical information on each adalimumab product, and status updates on the development of biosimilars going back as early as 2013 [47]. A new, national approach to tendering was set up with multiple winners, where depending on the competitiveness of the bid, the company has access to a greater or smaller part of the market, which was divided into 11 regions [48]. Each region has access to the originator product as well as preferred biosimilars. Also in Scotland switching plans were discussed before loss of exclusivity rights on Humira® and uptake statistics are shared monthly with health boards to benchmark their progress. One year after the introduction of adalimumab biosimilars in Europe, IQVIA reports biosimilar adalimumab market shares of 76% for the UK [49].

Several limitations can be attributed to this study. First, we did not conduct interviews for all regions in England and have only interviewed one person per region. However, information obtained during the interviews also covered regions for which no specific interview was carried out. In addition, questions mainly pertained to objective information on how a region approached the adoption of biosimilars, minimizing the need to conduct multiple interviews per region. Second, no local interviews were carried out with health boards in Scotland and Wales. However, these countries are far less populated than England, and one of the ten regions in England can cover as many people as the population in Scotland or Wales. Therefore, an alternative approach to ours could be to look at Scotland and Wales as additional regions on their own. Third, as it is difficult to quantify the influence of certain factors such as good relationships between stakeholders, we had to rely on qualitative information obtained during the interviews and a few published position statements and case studies. Also, other factors than the ones we identified might potentially influence originator/biosimilar market dynamics. Nonetheless, the value of information from qualitative research should not be underestimated as this is often the only way to learn how policy measures affect stakeholder perceptions and behaviour, since information on local initiatives and implementation processes are often not published or quantifiable.

Future research should continue to investigate barriers and best practice case studies for the adoption of biosimilars to generate learnings on originator/biosimilar market dynamics. Results of this study could be used as a starting point to look at other therapeutic classes and molecules, including less complex biologicals (e.g. insulin, filgrastim). In particular, the case of late entrants for molecules with established biosimilars and how policy measures and local practices develop for possible biosimilar to biosimilar switching is as yet not well documented. With the entry of adalimumab biosimilars, dynamics in the TNF-α inhibitors class could be reinvestigated. In addition, the entry of oncology biosimilars provides a new opportunity to gain knowledge on how biosimilars are implemented into clinical practice under different disease conditions.

5 Conclusion

By revisiting the history of infliximab and etanercept biosimilar adoption in healthcare regions in England, Scotland and Wales, we identified factors characterizing early and late adopters. The main driver for all regions to use biosimilars was the savings potential. Regions with a proactive attitude,

good stakeholder relationships leading to gain share agreements, and clinician engagement were identified as early adopters.

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Declarations

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Conflict of interest SS, IH and AGV are founders of the KU Leuven Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL). SS, IH and AV have conducted biosimilar research sponsored by Hospira (now Pfizer). SS was involved in a stakeholder roundtable on biologics and biosimilars sponsored by Amgen, Pfizer and MSD; he has participated in advisory board meetings for Pfizer and Amgen; and he has contributed to studies on biologics and biosimilars for Celltrion, Mundipharma and Pfizer. AV is involved in consulting, advisory work and speaking engagements for a number of companies, a.o. AbbVie, Accord Healthcare, Amgen, Biogen, Fresenius-Kabi, Medicines for Europe, Pfizer/Hospira, Mundipharma, Roche, Samsung/Bioepis, Sandoz/Novartis. EM, JK, RB, LM and TV declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Availability of data and material The market data used in this study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Ethics approval The interview guide and methodology for this study (MP006423) was approved by the Research Ethics Committee UZ/KU Leuven on 28 August 2018.

Author contributions IH, AV, SS and EM developed the idea for and were involved in the design of this study. EM, JK, RB, LM and TV were involved in data collection. EM drafted the initial version of the manuscript. IH, AV, SS, JK, RB, LM and TV critically reviewed the manuscript. All authors read and approved the final manuscript.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish Informed consent was obtained from all individual participants included in the study.

References

1. Download medicine data|European Medicines Agency: European Medicines Agency; 2020. https://www.ema.europa.eu/en/medicines/download-medicine-data. Accessed Aug 2020.
2. Commissioning framework for biological medicines (including biosimilar medicines): NHS England; 2017. https://www.england.nhs.uk/publication/commissioning-framework-for-biological-medicines/. Accessed Mar 2020.
3. Troein P, Newton M, Patel J, Scott K. The impact of biosimilar competition in Europe. IQVIA; 2019.
4. Moorkens E, Simoens S, Troein P, Declerck P, Vulto AG, Huys I. Different policy measures and practices between Swedish counties influence market dynamics: part 1-biosimilar and originator infliximab in the hospital setting. BioDrugs. 2019;33(3):285–97. https://doi.org/10.1007/s40259-019-00345-6.
5. Moorkens E, Simoens S, Troein P, Declerck P, Vulto AG, Huys I. Different policy measures and practices between Swedish counties influence market dynamics: part 2-biosimilar and originator etanercept in the outpatient setting. BioDrugs. 2019;33(3):299–306. https://doi.org/10.1007/s40259-019-00346-5.
6. Alnahar S, Elliott RA, Smith MD. Biosimilar uptake by British local formularies: a cross sectional study. Int J Clin Pharm. 2017;39(5):1055–60. https://doi.org/10.1007/s11096-017-0523-6.
7. Flume M. Biosimilars—best practice models in Germany. In: 15th Biosimilar Medicines conference (Medicines for Europe). London; 2017.
8. Marciano I, Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, et al. How did the introduction of biosimilar filgrastim influence the prescribing pattern of granulocyte colony-stimulating factors? Results from a multicentre, population-based study, from five Italian centres in the years 2009–2014. BioDrugs. 2016;30(4):295–306. https://doi.org/10.1007/s40259-016-0175-4.
9. Marciano I, Ingrasciotta Y, Giorgianni F, Ientile V, Chinellato A, Tari DU, et al. Pattern of use of biosimilar and originator somatropin in Italy: a population-based multiple databases study during the years 2009–2014. Front Endocrinol (Lausanne). 2018;9:95. https://doi.org/10.3389/fendo.2018.00095.
10. Moorkens E, Vulto AG, Huys I, Dylst P, Godman B, Keuerleber S, et al. Policies for biosimilar uptake in Europe: an overview. PLoS One. 2017;12(12):e0190147. https://doi.org/10.1371/journal.pone.0190147.
11. The NHS saves £324 million in a year by switching to better value medicines: NHS England; 2018. https://www.england.nhs.uk/2018/07/nhs-saves-324-million-year-switching-to-better-value-medicines/. Accessed Mar 2020.
12. Defined Daily Dose (DDD): World Health Organization; 2020. https://www.who.int/medicines/regulation/medicines-safety/toolkit_ddd/en/. Accessed May 2020.
13. WHOCC—ATC/DDD Index: World Health Organization; 2019. https://www.whocc.no/atc_ddd_index/?showdescription=yes&code=L04AB01. Accessed May 2020.
14. Prescribing and Medicines|Prescribing Datamarts|Health Topics|ISD Scotland: Public Health Scotland; 2020. https://www.isdscotland.org/Health-topics/Prescribing-and-medicines/Prescribing-Datamarts/. Accessed Oct 2020.
15. Strategic health authorities to be reduced to 10. Pharm J. 2006;467. https://www.pharmaceutical-journal.com/news-and-analysis/news/strategic-health-authorities-to-be-reduced-to-10/10021584.article?firstPass=false

16. Supporting Information: Strategic Health Authority: NHS Digital; 2019. https://www.datadictionary.nhs.uk/data_dictionary/nhs_business_definitions/s/strategic_health_authority_de.asp?shownav=1. Accessed Mar 2020.
17. The Local Health Boards (Area Change) (Wales) (Miscellaneous Amendments) Order 2019: NHS Wales; 2019. http://www.legislation.gov.uk/wsi/2019/349/made. Accessed Apr 2020.
18. Brinkmann S. Unstructured and semi-structured interviewing. In: Leavy P, editor. The Oxford handbook of qualitative research. New York: Oxford University Press; 2014.
19. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol. 2013;13:117. https://doi.org/10.1186/1471-2288-13-117.
20. Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. BMJ. 2000;320(7227):114–6.
21. Cylus J, Richardson E, Findley L, Longley M, O'Neill C, Steel D. United Kingdom: health system review. Health Syst Transit. 2015;17(5):1–125.
22. Search Results biosimilar—SPS—Specialist Pharmacy Service—the first stop for professional medicines advice: Specialist Pharmacy Service; 2020. https://www.sps.nhs.uk/?s=biosimilar. Accessed Apr 2020.
23. Razanskaite V, Bettey M, Downey L, Wright J, Callaghan J, Rush M, et al. Biosimilar infliximab in inflammatory bowel disease: outcomes of a managed switching programme. J Crohns Colitis. 2017;11(6):690–6. https://doi.org/10.1093/ecco-jcc/jjw216.
24. NHSScotland—How it worksIour NHS Scotland: NHS Scotland; 2020. http://www.ournhsscotland.com/our-nhs/nhsscotland-how-it-works. Accessed Mar 2020.
25. Biosimilar Medicines: A National Prescribing Framework: Healthcare Improvement Scotland; 2015. http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/programme_resources/idoc.ashx?docid=d51b3ae6-28b1-4b29-be88-64f5661e0038&version=-1. Accessed Mar 2020.
26. Biosimilar Medicines: A National Prescribing Framework: Healthcare Improvement Scotland; 2018. http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/programme_resources/biosimilar_medicines_framework.aspx. Accessed Mar 2020.
27. Optimising the safe and effective use of biological medicines: Healthcare Improvement Scotland; 2016. http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/adtc_resources/biosimilar_meds_case_studies.aspx. Accessed Mar 2020.
28. Secondary Care National Therapeutic Indicators 2018/19: NHS Scotland; 2018. https://www.therapeutics.scot.nhs.uk/resources/. Accessed Mar 2020.
29. Secondary Care National Prescribing Indicators 2016–2017: All Wales Medicines Strategy Group; 2016. http://www.awmsg.org/awmsgonline/docs/awmsg/medman/Secondary%20Care%20National%20Prescribing%20Indicators%202016-2017.pdf. Accessed Mar 2020.
30. Resources: All Wales Therapeutics and Toxicology Centre; 2020. https://www.awttc.org/wapsu/resources. Accessed Mar 2020.
31. Best Practice Day 2017: All Wales Therapeutics and Toxicology Centre; 2017. https://www.awttc.org/news/best-practice-day-2017. Accessed Mar 2020.
32. Biosimilar Best Practice Day: All Wales Therapeutics and Toxicology Centre; 2019. https://www.awttc.org/news/biosimilar-best-practice-day. Accessed Mar 2020.
33. Ayas SM. Position statement on biosimilars: Aneurin Bevan University Health Board; 2015. http://www.wales.nhs.uk/sites3/Documents/814/BIOSIMILARS-ABUHBpositionStatement%5BNov2015%5D.pdf. Accessed Mar 2020.
34. Biosimilar Strategy: Abertawe Bro Morgannwg University Health Board; 2018. http://www.wales.nhs.uk/sitesplus/documents/863/18-F-024%20Biosimilar%20Strategy.pdf. Accessed Mar 2020.
35. Chapman SR, Fitzpatrick RW, Aladul MI. What drives the prescribing of growth hormone preparations in England? Prices versus patient preferences. BMJ Open. 2017;7(4):e013730. https://doi.org/10.1136/bmjopen-2016-013730.
36. 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(6):e016730. https://doi.org/10.1136/bmjopen-2017-016730.
37. 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(6):533–44. https://doi.org/10.1007/s40259-017-0252-3.
38. 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(5):439–46. https://doi.org/10.1007/s40259-017-0238-1.
39. Aladul MI, Fitzpatrick RW, Chapman SR. Healthcare professionals' perceptions and perspectives on biosimilar medicines and the barriers and facilitators to their prescribing in UK: a qualitative study. BMJ Open. 2018;8(11):e023603. https://doi.org/10.1136/bmjopen-2018-023603.
40. Aladul MI, Fitzpatrick RW, Chapman SR. Differences in UK healthcare professionals' knowledge, attitude and practice towards infliximab and insulin glargine biosimilars. Int J Pharm Pract. 2019;27(2):214–7. https://doi.org/10.1111/ijpp.12485.
41. 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(3):310–7. https://doi.org/10.1016/j.sapharm.2018.05.009.
42. CCG Biosimilars National Questionnaire Report: NHS England; 2018. https://www.sps.nhs.uk/wp-content/uploads/2018/10/CSUs_CCGsBiosimilarsUptakeSurveyApril2018.pdf. Accessed Mar 2020.
43. Biosimilars uptake survey report—20 NHS Trusts: NHS England; 2018. https://www.sps.nhs.uk/wp-content/uploads/2018/10/CSUs_TrustsBiosimilarsUptakeSurveyApril2018.pdf. Accessed Mar 2020.
44. Moorkens E, Barcina T, Vulto A, Schulz M, Gradl G, Enners S, et al. Learnings from regional market dynamics of originator and biosimilar infliximab and etanercept in Germany. Pharmaceuticals. 2020. https://doi.org/10.3390/ph13100324.
45. Moorkens E, Vulto AG, Huys I. Biosimilars in Belgium: a proposal for a more competitive market. Acta Clin Belg. 2020. https://doi.org/10.1080/17843286.2020.1761690.
46. Khan D, Luig T, Mosher D, Campbell-Scherer D. Lessons from international experience with biosimilar implementation: an application of the diffusion of innovations model. Healthc Policy. 2020;15(3):16–27. https://doi.org/10.12927/hcpol.2020.26133.
47. Adalimumab: Specialist Pharmacy Service; 2016 [updated 26/03/2020]. https://www.sps.nhs.uk/medicines/adalimumab/. Accessed Apr 2020.
48. Commissioning intentions: adalimumab: NHS England; 2018. https://www.sps.nhs.uk/wp-content/uploads/2018/09/20180925-Contractual-Commissioning-Intentions-Adalimumab_corporate-template.pdf. Accessed Jan 2020.
49. IQVIA MIDAS MTH October 2019. IQVIA; 2019.
50. Vanhove T. Biosimilars: how can we explain regional variations in their use?—the United Kingdoms originator biological and biosimilar market: infliximab and etanercept. Leuven: KU Leuven; 2019.

51. What is a Biosimilar Medicine?: NHS England; 2015. https://www.gov.uk/government/publications/what-is-a-biosimilar-medicine. Accessed Mar 2020.
52. What is a Biosimilar Medicine?: NHS England; 2019. https://www.england.nhs.uk/publication/what-is-a-biosimilar-medicine/. Accessed Mar 2020.
53. Evaluating biosimilar medicines: National Institute for Health and Care Excellence (NICE); 2015. https://www.nice.org.uk/news/article/evaluating-biosimilar-medicines. Accessed Dec 2020.
54. Biosimilar medicines—key therapeutic topic: NICE; 2016. https://www.nice.org.uk/advice/ktt15. Accessed Mar 2020.
55. Bioequivalence between biosimilar and reference tumour necrosis factor–alpha inhibitors: NICE; 2017. arms.evidence.nhs.uk/resources/hub/1058807/attachment. Accessed Apr 2020.
56. NHS England» 2017–2019 Prescribed Services CQUIN Schemes: NHS England; 2016. https://www.england.nhs.uk/nhs-standard-contract/cquin/pres-cquin-17-19/. Accessed June 2020.
57. Regional Medicines Optimisation Committees Operating Model: NHS England; 2019. https://www.england.nhs.uk/publication/regional-medicines-optimisation-committee-operating-guidance-and-recruitment-information/. Accessed Apr 2020.
58. Cancer Vanguard: The Cancer Vanguard; 2015. https://cancervanguard.nhs.uk/about/. Accessed Apr 2020.
59. Biosimilars—Getting it right first time: The Cancer Vanguard; 2017. https://cancervanguard.nhs.uk/biosimilars-getting-it-right-first-time/. Accessed Apr 2020.