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Survey of the UK healthcare professionals' knowledge, attitude and practice towards infliximab and insulin glargine biosimilars

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Abstract

Objective: To investigate health care professionals' knowledge and attitude towards infliximab and insulin glargine biosimilars and the factors influencing their prescribing. Then, to compare health care professionals' attitudes with the utilisation of these biosimilars in UK hospitals.

Design: Self-administered, one-time web-based survey and drug utilisation analysis.

Setting and data sources: Professional associations and societies in the field of dermatology, diabetology, gastroenterology and rheumatology in the UK, between 8th of August 2016 to 8th of January 2017. The volume of utilisation of branded and biosimilar infliximab and insulin glargine in UK hospitals was derived from the DEFINE database, between 2015 and 2016.

Outcomes: Participants' knowledge and awareness of biosimilars and factors influencing their use and corresponding usage of infliximab and insulin glargine biosimilars.

Results: Responses were obtained from 234 healthcare professionals across dermatology, diabetology, gastroenterology and rheumatology specialties. 75% of respondents were aware that biosimilars were available on their local formulary. 77% of respondents considered biosimilars extremely or very important to save costs for the NHS. Gastroenterologists had the highest utilisation of infliximab biosimilars (14%) in 2015 rising to (62%) in 2016. Healthcare professionals had greater concerns about safety and efficacy when switching patients to biosimilars than when starting biosimilars in biologic naïve patients. Guidance from NICE and robust pharmacovigilance studies on biosimilars were both considered important factors in increasing biosimilars use.

Conclusion: British healthcare professionals are well informed about biosimilars with high level of awareness. Safety and efficacy concerns were higher in switching than in initiating biosimilars among prescribers. More robust pharmacovigilance studies on biosimilars similarity and national guidance were required to increase their prescribing of biosimilars.

Strengths and limitations of study

- *First study of UK HCPs knowledge and attitudes to biosimilars and the first to consider the perceptions of safety and efficacy when switching from a branded biologic or starting a biosimilar de novo.*
- *HCPs' attitudes are compared and contrasted with the utilisation of biosimilars in different specialties.*
- *Survey responses from the professional associations were variable and most of the respondents were consultants/registrars.*

Introduction

Biosimilars are a non-branded copy of approved and patent expired biological medicines. [1] The emergence of biosimilars means these less expensive biological medicines have the potential to produce cost savings for the NHS.[2] Since 2006, 23 biosimilars (corresponding to 9 active molecules) have been licensed in Europe, but the uptake of biosimilars has varied between countries.[3 4] It is possible that a variance in understanding amongst healthcare prescribers of the potential risks and benefits surrounding biosimilars may account for this varied uptake.[5] With the recent approval (2015-2017) of biosimilar "blockbuster drugs" such as infliximab, insulin glargine and etanercept in Europe and the subsequent potentially large cost savings to health systems, there has been an increased focus on this area of prescribing.[6] Branded monoclonal antibodies, such as adalimumab, rituximab and trastuzumab, now have competition from biosimilars manufacturers and there are a large number of biosimilars under development.[7] Thus, all health care professionals (HCPs) are likely to encounter patients for whom a biosimilar has been, or could be prescribed.[8]

The variance in uptake of biosimilars suggests that despite a wealth of clinical and scientific literature, regulatory documents, and expert opinion, HCPs may still have some reservations about using these medicines.

A survey of the literature revealed only 12 studies on HCPs knowledge and understanding on biosimilars and no previous study conducted among HCPs in the UK, which is considered a relatively large market for biological and generic medicines and a potentially attractive market for the biosimilars.[9-20] Only three out of the 12 available studies were conducted in Europe. Narayanan and Liu (2013) and Narayanan and Nag (2016),[11 18] focused on the likelihood of use of biosimilars among rheumatologists, while, Danese et al., (2016) focused on the change in knowledge of biosimilar among inflammatory bowel disease specialists. None of the retrieved studies focused or compared HCPs concerns about safety and efficacy when considering starting biosimilars or switching patients to biosimilars.[17] To fill this gap in knowledge this study aimed to explore UK HCPs' knowledge, attitudes and practice towards biosimilars in general and compare and contrast the results with the utilisation of infliximab and insulin glargine biosimilars in hospitals in UK.

Methods

Survey design

This was a non-interventional, anonymised, self-administered, one-time web-based survey among HCPs in the UK. This survey was conducted over five months, from 8th of August 2016 to 8th of January 2017. This study approved by the Independent Peer Review Committee at Keele University.

Survey sample

Specialists (consultants, registrars, pharmacists and nurses) in dermatology, diabetology, gastroenterology and rheumatology who were registered members of the British Society of Gastroenterology, the British Society of Paediatric Gastroenterology Hepatology and Nutrition, the Welsh Association for Gastroenterology & Endoscopy, the British Society for Medical Dermatology, the British Society for Paediatric Endocrinology and Diabetes, the Association of British Clinical Diabetologists, the British Dermatological Nursing Group, the Scottish Society for Rheumatology, the British Society for Rheumatology.

Survey procedure

The survey was a closed survey. A request to distribute an invitation to participate in this web-survey was emailed to the professional associations and societies. The invitation letter included a link to the web survey. Reminder emails were sent via the professional associations at four weeks after the initial mailing. The survey front page includes information, describing the survey and asking for their voluntary participation. By reading and responding they gave their consent. The survey questionnaires were designed in such a way that it could not be submitted until all questions had been answered. All the respondents were able to review and change their responses by scrolling up and down the page before submission. Cookies were used by the survey tool allowing only one response per computer.

Survey questionnaire

An 11 question questionnaire was developed from emerging themes in the current literature on biosimilars and designed using an electronic website (Survey Monkey). The EBSCOhost online research database and PubMed online research database were searched using the terms healthcare professional,

physician, doctor, clinician, consultant, registrar, general practitioner, pharmacist, nurse, rheumatologist, gastroenterologist, endocrinologist, diabetologist, dermatologist, survey, web-survey, knowledge, attitude, awareness, perception, opinion, experience, behaviour, practice, biosimilar, subsequent entry biologic and me too biologic. Questions were developed to investigate knowledge, experience and opinions towards biosimilars. The survey was piloted on a small number of HCPs and revised appropriately to eliminate redundancy and difficult or ambiguous questions. Questionnaires were not asking any personally identifying information.

Utilisation data

Data on infliximab and insulin glargine utilisation by speciality in UK hospitals (Figure 3) were taken from DEFINE Software since the introduction of infliximab and insulin glargine biosimilars in March and September 2015 respectively to December 2016. The DEFINE Software is a NHS prescribing database of medicines usage which collects data from approximately 120 hospitals who subscribe to the software package (covering over 90% of NHS hospitals throughout the UK including Specialist Centres and Mental Health Trusts).[21]

Statistical analysis

The survey responses to individual questions were collected, summarised as number and percentage of responding HCPs using Survey Monkey and Microsoft Excel 2013. The percentage of infliximab and insulin glargine biosimilars uptake was calculated using Microsoft Excel 2013.

Results

Characterisation of participants

A total of 234 HCPs participated in the survey and responses were relatively evenly distributed between the various specialities. The majority of responses (64%) (n=150) were from consultants and registrars. Most of the survey participants 64% (n=150) were general hospital based HCPs, followed by tertiary centre based HCPs 30% (n=70), while the remaining were primary care based or in other settings 6% (n=14) (Table 1).

Table 1 Characteristics of participants

Characteristics		Percentage	Number
Profession	Consultants and registrars	64%	150
	Pharmacists	11%	26
	Nurses	25%	58
Speciality	Dermatology	26%	61
	Diabetology	25%	58
	Gastroenterology	23%	54
	Rheumatology	26%	61
Work setting	Primary care	4%	9
	General hospitals	64%	150
	Tertiary centres	30%	70
	Other settings	2%	5

Knowledge and awareness of biosimilars

Most survey participants (72%) thought biosimilars were similar copies of biological medicines, 18% thought they were generic biological medicines, 1% had thought they were new biological medicines and 3% thought they were counterfeit medicines. A minority (3%) stated that they had heard about biosimilars but did not know what they were, and 3% had never heard about biosimilars. A large

proportion of the respondents (75%) were aware that biosimilars were available on their local formulary (Table 2).

Table 2 participants' knowledge and awareness

Question	Answer	Percentage	Number
Which statement best describes what you understand a biosimilar to be…	A similar copy of a biological medicine	72%	168
	A generic biological medicine	18%	42
	A counterfeit copy of a biological medicine	3%	6
	A new biological medicine	1%	3
	I have heard about biosimilars but I do not know what they are	3%	8
	I have never heard about biosimilars	3%	7
Are biosimilars on your local formulary?	Yes	75%	174
	No	9%	21
	I do not know	15%	36
	Not applicable	1%	2

Importance of biosimilars prescribing
Cost saving was the dominant consideration when prescribing biosimilars (Figure 1).

Frequency of prescribing biosimilars
Gastroenterology consultants were the most frequent prescribers of biosimilars (daily and weekly), followed by rheumatologists and diabetologists. Dermatologists prescribed biosimilars the least frequently (Figure 2).

Utilisation of infliximab and insulin glargine
Analysis of the utilisation of branded and biosimilar infliximab and insulin glargine by speciality in UK hospitals showed that compared to other specialties gastroenterologists had the highest utilisation of infliximab biosimilars (14%) in 2015 rising to (62%) by 2016. By contrast, dermatologists had the lowest utilisation of infliximab biosimilars (6%) in 2015 and (35%) in 2016. Diabetologists' utilisation of insulin glargine biosimilar (0.5%) in 2015 and (9%) in 2016 were the least in comparison with the utilisation of infliximab biosimilars by HCPs (Figure 3).

Perception of safety and efficacy
The majority of gastroenterology consultants had no or minor concerns about the safety (95%) and efficacy (90%) of biosimilars when initiating treatment or when switching patients (95%), (93%) respectively. Although a large proportion of rheumatology consultants also had no or minor concerns about safety and efficacy when initiating treatment (92%), (88%) respectively, they had major concerns/concerns about safety (55%) and efficacy (64%) that inhibited them switching patients to biosimilars (Figure 4).

Factors increasing the use of biosimilars
Respondents weighted National Institute for Health and Care Excellence (NICE) guidance and robust pharmacovigilance studies on biosimilars equally likely to increase their use of biosimilars. Factors such as local policy, potential cost saving to their organisation and robust cost-effectiveness data for biosimilars versus branded biosimilar medicines were only marginally less important. Cost saving to the respondents' organisation influenced prescribing whether or not these saving were invested in the prescribers' department (Figure 5).

Discussion

Most of UK HCPs that responded (72%) understood correctly what biosimilars were. A minority thought they were new biologics (1%) or generics (18%) and only 6% did not know what biosimilars were (Table 2). Our result show that UK HCPs have a comparable level of knowledge about biosimilars to US specialty physicians and a higher level in comparison with Canadian and French rheumatologists and Ukrainian physicians.[12 13 15 20] Despite this high level of understanding, early prescribing trends of infliximab biosimilars (November, 2015) in the UK showed that they were being prescribed in only 45% of Acute Trusts with a varied degree of uptake among these Trusts.[22] Our results show infliximab biosimilar usage in NHS hospitals rose from 11% in 2015 to 55% in 2016 (Figure 3). This considerable increase most likely reflects the views of the majority of HCPs in our study who considered biosimilars prescribing as important for saving costs to the NHS. Given the existing financial pressures within the NHS this is likely to be a potent driver of prescribing. This is in line with Beck's et al findings that 71% of French rheumatologists strongly agreed that biosimilars saved costs for their health services.[15] This financial driver is also implicit in our findings that HCPs held the view that biosimilars are important to stimulate competition in the biological medicine market, since cost competition may lead to downward pressure on prices thus saving costs.[23]

Our survey highlighted a variance in acceptance and utilisation of biosimilars between specialties, with gastroenterologists the most positive followed by rheumatologists and diabetologists with dermatologists the least accepting (Figures 2 and 3). This may be due to published guidance from the British Society of Gastroenterology that supported both initiation and switching to biosimilar infliximab.[24] Our findings are in line with the result of a survey of the American Gastroenterological Association, which found that 72% of gastroenterologists were likely to prescribe biosimilars.

The European Medicine Agency biosimilar approval process involves comparison of the safety and efficacy profiles of biosimilars to their reference biological product.[38] Nonetheless, HCPs' own perception of the safety and efficacy of biosimilars influenced whether they considered starting a new patient or switching a patient to a biosimilar.[39] Our survey showed that gastroenterologist consultants have less concerns about safety and efficacy during initiating and switching to biosimilars than other specialties (Figure 4), which is in line with the European Crohn's Colitis Organisation survey in 2016 that showed that only a minority of inflammatory bowel disease specialists felt little or no confidence in the use of biosimilars.[40]

Whilst rheumatology consultants were similarly less concerned about efficacy and safety in infliximab naïve patients (Figure 4), they expressed more major concerns than other specialties when switching patients from a branded biologic medicine to a biosimilar. This cautious approach is also evident in the European League Against Rheumatism report (2016) which stated that patients who develop antibodies against Remicade® were less likely to benefit from infliximab biosimilars and not suitable for switching.[41]

A survey of French rheumatologists showed (88%) were prepared to prescribe biosimilars to biologic naïve patient,[15] whereas a survey of European rheumatologists showed only 50% likely to prescribe biosimilars.[36,11] Canadian rheumatologists are even more cautious than their European counterparts stating they were very unlikely or unlikely to prescribe a biosimilars to a biologic naïve patient.[13] Interestingly a survey among US, France and Germany specialty physicians showed that diabetologists/endocrinologists were the least likely to prescribe biosimilars which is similar to the UK results.[37] From the UK survey, it is possible to postulate that HCPs concerns about biosimilars could be alleviated by publishing more robust pharmacovigilance studies on biosimilars similarity and guidance from trusted and reputable bodies such as NICE, as well as reinvesting potential savings in local organisations. These results reflect the findings of other European studies.[15 42]

The strength of this study was that we were able to compare and contrast HCPs' attitude toward biosimilars with actual utilisation data. Our study has some limitations. The responses from the professional associations were variable and most of the respondents were consultants/registrars. Only consultants'/registrars' data was used to interpret safety and efficacy concerns (Figures 2 and 3) to prevent the results being skewed by non-prescribing health care professionals (it is not possible to elicit from the survey whether or not pharmacists and nurses were prescribers). Unfortunately, it was not possible to calculate the response rate as the total number of members of the professional associations and societies are confidential and some HCPs were registered in more than one association or society.

Conclusion

UK HCPs have a good understanding of biosimilars and consider biosimilars important as a cost saving measure. There is significant variation between specialties in their attitude to using biosimilars which is also reflected in actual utilisation data. Gastroenterologists and Rheumatologists are more likely to initiate a biosimilar than other specialties but rheumatologists have more concerns than

gastroenterologists when switching patients. Despite both groups claiming to be influenced by national guidance from NICE, it is probable that discipline specific guidance for gastroenterologists influenced their responses.

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Access to data: All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval: This study approved by the Independent Peer Review Committee at Keele University (Reference 421).

Data sharing statement: Data collected from survey is anonymised. The raw data from which result paper are derived can be made available on request.

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Figure 1 Respondents were asked "how important are the following factors when considering prescribing a biosimilar?"

Figure 2 Respondents (consultants) were asked "how often do you prescribe biosimilars?"

Figure 3 Branded and biosimilar infliximab and insulin glargine utilisation by speciality in UK hospitals between 2015 and 2016
* Reference biological medicine: includes infliximab in dermatology, gastroenterology and rheumatology speciality and insulin glargine in diabetology speciality
**Biosimilar(s): includes infliximab biosimilars (Inflectra and Remsima)® and insulin glargine biosimilar (Abasaglar)®, (Flixabi® and Lusduna® were not included as they have not been used yet in the UK).

Figure 4 Respondents (consultants) were asked "how concerned are you about safety and efficacy when considering starting or switching to biosimilars?"
A: Starting new patients - Safety concerns. B: Starting new patients - Efficacy concerns. C: Switching patients - Safety concerns. D: Switching patients - Efficacy concerns.

Figure 5 Respondents were asked "How likely are the following factors to increase your use of biosimilars?"

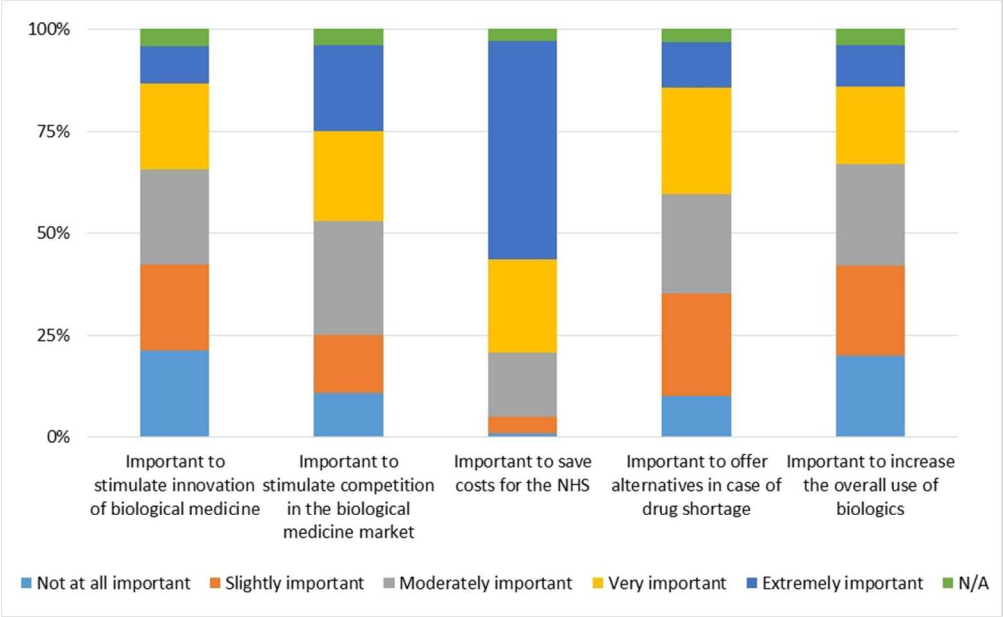

Figure 1 Respondents were asked "how important are the following factors when considering prescribing a biosimilar?"

82x50mm (300 x 300 DPI)

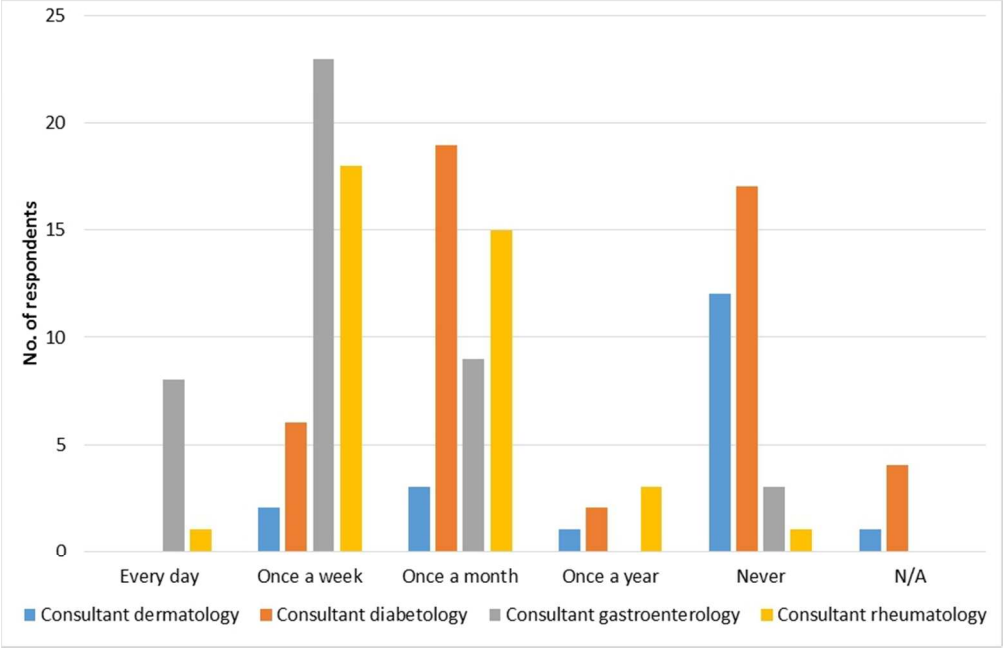

Figure 2 Respondents (consultants) were asked "how often do you prescribe biosimilars?"

78x50mm (300 x 300 DPI)

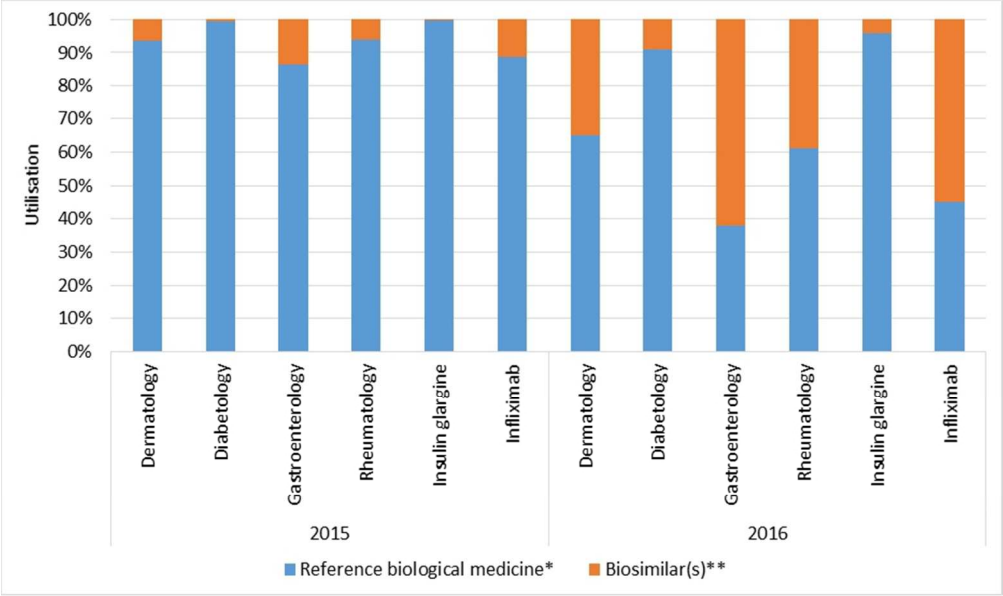

Figure 3 Branded and biosimilar infliximab and insulin glargine utilisation by speciality in UK hospitals between 2015 and 2016

* Reference biological medicine: includes infliximab in dermatology, gastroenterology and rheumatology speciality and insulin glargine in diabetology speciality

**Biosimilar(s): includes infliximab biosimilars (Inflectra and Remsima)® and insulin glargine biosimilar (Abasaglar)®, (Flixabi® and Lusduna® were not included as they have not been used yet in the UK).

78x46mm (300 x 300 DPI)

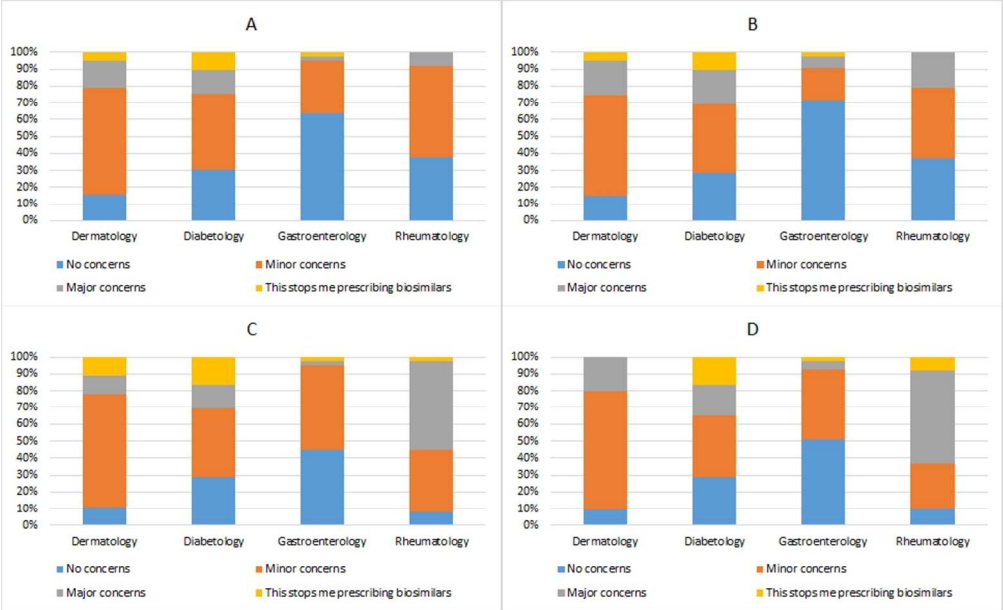

Figure 4 Respondents (consultants) were asked "how concerned are you about safety and efficacy when considering starting or switching to biosimilars?"
A: Starting new patients - Safety concerns. B: Starting new patients - Efficacy concerns. C: Switching patients - Safety concerns. D: Switching patients - Efficacy concerns.

132x80mm (300 x 300 DPI)

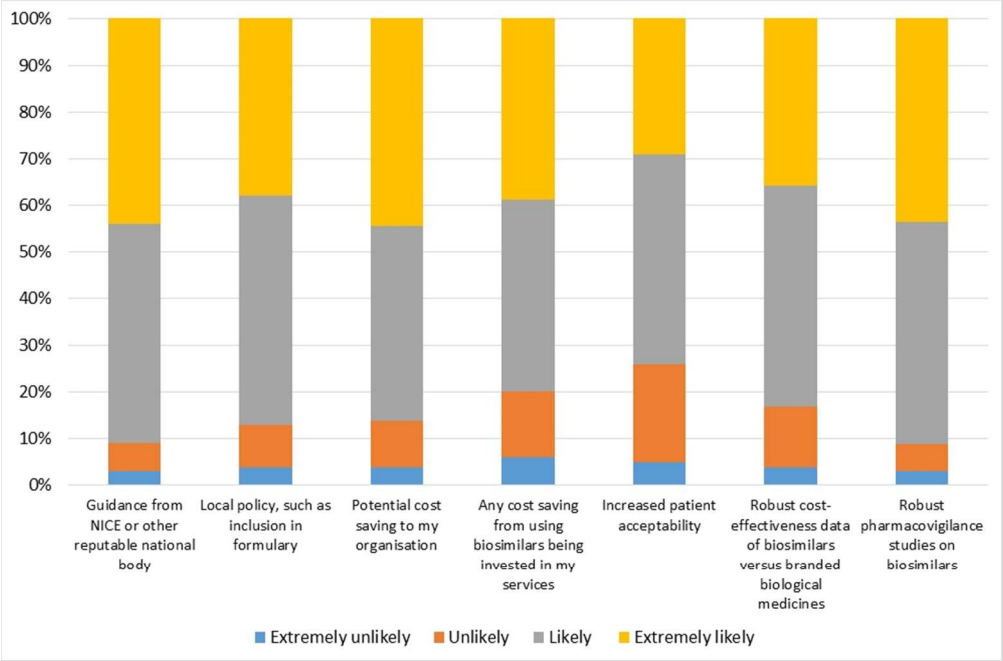

Figure 5 Respondents were asked "How likely are the following factors to increase your use of biosimilars?"

84x55mm (300 x 300 DPI)

Checklist for Reporting Results of Internet E-Surveys (CHERRIES)

Item category	Page	Explanation
Design	**3**	This was a non-interventional, anonymised, self-administered, one-time web-based survey among HCPs in the UK.
IRB	**3**	**Approval.** The study has been approved by Keele University.
	3	**Informed consent.** The survey front page includes information, describing the survey and asking for their voluntary participation. By reading and responding they gave their consent.
	4	**Data protection.** No personally identifying information was collected.
Development and pretesting	**3-4**	Survey questionnaire was developed from emerging themes in the current literature on biosimilars. The survey was piloted on a small number of HCPs and revised appropriately to eliminate redundancy and difficult or ambiguous questions.
Recruitment process	**3**	**Survey type.** The survey was a closed survey where the participants view the survey instrument until they click on the link appended in the contact email.
	3	**Contact mode.** Contact made through the relevant professional associations.
	3	**Advertising the survey.** As above, the survey was advertised through the relevant professional associations.

Survey administration	**3**	**Web/E-mail.** The survey covering letters were sent to the relevant societies and association to forward by email to the registered HCPs. The survey link was appended to the bottom of the e-mail cover letter. Upon clicking the survey link the participants were directed to the online survey.
	3	**Context.** Context and background were provided in the covering letter and information sheet and through professional associations.
	3	**Mandatory/voluntary.** The survey was voluntary.
		Incentives. None.
	3	**Time/Date.** August 2016 and January 2017.
		Randomization of items or questionnaire. N/A
	4	**Adaptive questioning.** Question were adapted after the pilot phase.
	3	**Number of items.** 11 items.
		Number of screens. 2 screens.
		Completeness check. The survey tool was designed in such a way that it could not be submitted until all questions had been answered.
	3	**Review step.** All the respondents were able to review and change their responses by scrolling up and down the page before submission.
Response rates		**Unique site visitor. N/A**
		View rate. N/A
	6	**Participation rate.** Participation rate was not calculated.
		Completion rate. All of the participants (100%) that agreed to participate finished the survey.

Preventing multiple entries	**3**	**Cookies used.** Cookies were used by the survey tool allowing only one response per computer. **IP check.** IP addresses were not collected. **Log file analysis.** The study did not include a log file analysis. **Registration.** The survey was a closed survey where the participants viewed the survey instrument until they clicked on the link appended in the contact email.
Analysis		**Handling of incomplete surveys.** This feature was not applied in the survey since the survey tool only accepted completed survey forms **Questionnaires submitted with an atypical timestamp.** N/A **Statistical correction.** N/A

BMJ Open

Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: Result of a UK web-based survey

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Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: Result of a UK web-based survey

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KEY WORDS- Biosimilars, infliximab, insulin glargine, healthcare professionals, knowledge, attitude

WORD COUNT: 2577

Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: Result of a UK web-based survey

Abstract

Objective: To investigate health care professionals' knowledge and attitude towards infliximab and insulin glargine biosimilars and the factors influencing their prescribing. Then, to compare health care professionals' attitudes with the utilisation of these biosimilars in UK hospitals.

Design: Self-administered, one-time web-based survey and drug utilisation analysis.

Setting and data sources: Professional associations and societies in the field of dermatology, diabetology, gastroenterology and rheumatology in the UK, between 8th of August 2016 to 8th of January 2017. The volume of utilisation of branded and biosimilar infliximab and insulin glargine in UK hospitals was derived from the DEFINE database, between 2015 and 2016.

Outcomes: Participants' knowledge and awareness of biosimilars and factors influencing their use and corresponding usage of infliximab and insulin glargine biosimilars.

Results: Responses were obtained from 234 healthcare professionals across dermatology, diabetology, gastroenterology and rheumatology specialties. 75% of respondents were aware that biosimilars were available on their local formulary. 77% of respondents considered biosimilars extremely or very important to save costs for the NHS. Gastroenterologists had the highest utilisation of infliximab biosimilars (14%) in 2015 rising to (62%) in 2016. Healthcare professionals had greater concerns about safety and efficacy when switching patients to biosimilars than when starting biosimilars in biologic naïve patients. Guidance from NICE and robust pharmacovigilance studies on biosimilars were both considered important factors in increasing biosimilars use.

Conclusion: British healthcare professionals are well informed about biosimilars with high level of awareness. Safety and efficacy concerns were higher in switching than in initiating biosimilars among some prescribers. It is probable that personal experience of biologics as well as discipline specific guidance influenced prescribers responses.

Strengths and limitations of study

- *First study of UK HCPs knowledge and attitudes to biosimilars and the first to consider the perceptions of safety and efficacy when switching from a branded biologic or starting a biosimilar de novo.*
- *HCPs' attitudes are compared and contrasted with the utilisation of biosimilars in different specialties.*
- *Survey responses from the professional associations were variable and most of the respondents were consultants/registrars.*

Introduction

Biosimilars are a non-branded copy of approved and patent expired biological medicines.[1] The emergence of biosimilars means these less expensive biological medicines have the potential to produce cost savings for the NHS.[2] Since 2006, 28 biosimilars (corresponding to 11 active molecules) have been licensed in Europe, but the uptake of biosimilars has varied between countries.[3, 4] It is possible that a variance in understanding amongst healthcare prescribers of the potential risks and benefits surrounding biosimilars may account for this varied uptake.[5] With the recent marketing (2015-2017) of biosimilar "blockbuster drugs" such as infliximab, insulin glargine, etanercept and rituximab, and the European Medicine Agency approval of adalimumab biosimilars (patent expiration in 2018) and the subsequent potentially large cost savings to health systems, there has been an increased focus on this area of prescribing.[3, 6] Thus, all health care professionals (HCPs) are likely to encounter patients for whom a biosimilar has been, or could be prescribed.[7]

The variance in uptake of biosimilars suggests that despite a wealth of clinical and scientific literature, regulatory documents, and expert opinion on early approved biosimilars (somatropin, epoetin and filgrastim), HCPs may still have some reservations about using these medicines and more recent biosimilars (infliximab and insulin glargine) in which clinical and non clinal studies on switching originator to biosimilar are required.

A survey of the literature revealed only 12 studies on HCPs knowledge and understanding on infliximab and insulin glargine biosimilars before and after their introduction (Figure 1), and no previous study conducted among HCPs in the UK, which is considered a relatively large market for biological and generic medicines and a potentially attractive market for the biosimilars.[8-19] Only three out of the 12 available studies were conducted in Europe. Narayanan and Liu (2013) and Narayanan and Nag (2016),[10, 17] focused on the likelihood of use of biosimilars among rheumatologists, while, Danese et al., (2016) focused on the change in knowledge of biosimilar among inflammatory bowel disease specialists. None of the retrieved studies focused or compared HCPs concerns about safety and efficacy when considering starting biosimilars or switching patients to biosimilars.[16] To fill this gap in knowledge this study aimed to explore UK HCPs' knowledge, attitudes and practice towards biosimilars in general and compare and contrast the results with the utilisation of infliximab and insulin glargine biosimilars in hospitals in UK.

Methods

Survey design

This was a non-interventional, anonymised, self-administered, one-time web-based survey among HCPs in the UK. This survey was conducted over five months, from 8th of August 2016 to 8th of January 2017. This study approved by the Independent Peer Review Committee at Keele University.

Survey sample

Specialists (consultants, registrars, pharmacists and nurses) in dermatology, diabetology, gastroenterology and rheumatology who were registered members of the British Society of Gastroenterology, the British Society of Paediatric Gastroenterology Hepatology and Nutrition, the Welsh Association for Gastroenterology & Endoscopy, the British Society for Medical Dermatology, the British Society for Paediatric Endocrinology and Diabetes, the Association of British Clinical Diabetologists, the British Dermatological Nursing Group, the Scottish Society for Rheumatology, the British Society for Rheumatology.

Survey procedure

The survey was a closed survey. A request to distribute an invitation to participate in this web-survey was emailed to the professional associations and societies. The invitation letter included a link to the web survey. Reminder emails were sent via the professional associations at four weeks after the initial mailing. The survey front page includes information, describing the survey and asking for their voluntary participation. By reading and responding they gave their consent. The survey questionnaires were designed in such a way that it could not be submitted until all questions had been answered. All the respondents were able to review and change their responses by scrolling up and down the page before submission. Cookies were used by the survey tool allowing only one response per computer.

Survey questionnaire

An 11-question questionnaire was developed from emerging themes in the current literature on biosimilars and designed using an electronic website (Survey Monkey). The EBSCOhost online research database and PubMed online research database were searched using the terms healthcare professional, physician, doctor, clinician, consultant, registrar, general practitioner, pharmacist, nurse, rheumatologist, gastroenterologist, endocrinologist, diabetologist, dermatologist, survey, web-survey, knowledge, attitude, awareness, perception, opinion, experience, behaviour, practice, biosimilar, subsequent entry biologic and me too biologic. Questions were developed to investigate knowledge, experience and opinions towards biosimilars. The survey was piloted on a

small number of HCPs and revised appropriately to eliminate redundancy and difficult or ambiguous questions. Questionnaires were not asking any personally identifying information.

Utilisation data

Data on infliximab and insulin glargine utilisation by speciality in UK hospitals (Figure 4) were taken from DEFINE Software since the introduction of infliximab and insulin glargine biosimilars in March and September 2015 respectively to December 2016. The DEFINE Software is a NHS prescribing database of medicines usage which collects data from approximately 120 hospitals who subscribe to the software package (covering over 90% of NHS hospitals throughout the UK including Specialist Centres and Mental Health Trusts). [20]

Statistical analysis

The survey responses to individual questions were collected, summarised as number and percentage of responding HCPs using Survey Monkey and Microsoft Excel 2013. The percentage of infliximab and insulin glargine biosimilars uptake was calculated using Microsoft Excel 2013.

Results

Characterisation of participants

A total of 234 HCPs participated in the survey and responses were relatively evenly distributed between the various specialities. The majority of responses (64%) (n=150) were from consultants and registrars. Most of the survey participants 64% (n=150) were general hospital based HCPs, followed by tertiary centre based HCPs 30% (n=70), while the remaining were primary care based or in other settings 6% (n=14) (Table 1).

Table 1 Characteristics of participants

Characteristics		Percentage	Number
Profession	Consultants and registrars	64%	150
	Pharmacists	11%	26
	Nurses	25%	58
Speciality	Dermatology	26%	61
	Diabetology	25%	58
	Gastroenterology	23%	54
	Rheumatology	26%	61
Work setting	Primary care	4%	9
	General hospitals	64%	150
	Tertiary centres	30%	70
	Other settings	2%	5

Knowledge and awareness of biosimilars

Most survey participants (72%) thought biosimilars were similar copies of biological medicines, 18% thought they were generic biological medicines, 1% had thought they were new biological medicines and 3% thought they were counterfeit medicines. A minority (3%) stated that they had heard about biosimilars but did not know what they were, and 3% had never heard about biosimilars. A large proportion of the respondents (75%) were aware that biosimilars were available on their local formulary (Table 2).

Table 2 participants' knowledge and awareness

Question	Answer	Percentage	Number
Which statement best describes	A similar copy of a biological medicine	72%	168

what you understand a biosimilar to be…	A generic biological medicine	18%	42
	A counterfeit copy of a biological medicine	3%	6
	A new biological medicine	1%	3
	I have heard about biosimilars but I do not know what they are	3%	8
	I have never heard about biosimilars	3%	7
Are biosimilars on your local formulary?	Yes	75%	174
	No	9%	21
	I do not know	15%	36
	Not applicable	1%	2

Importance of biosimilars prescribing
Cost saving was the dominant consideration when prescribing biosimilars (Figure 2).

Frequency of prescribing biosimilars
Gastroenterology consultants were the most frequent prescribers of biosimilars (prescribing biosimilars every day or week), followed by rheumatologists and diabetologists. Dermatologists prescribed biosimilars the least frequently (Figure 3).

Utilisation of infliximab and insulin glargine
Analysis of the utilisation of infliximab by speciality in UK showed that compared to other specialties gastroenterologists had the highest utilisation of infliximab (67%), followed by rheumatologists (27%) and dermatologists (6%). Further Analysis of the utilisation of branded and biosimilar infliximab and insulin glargine by speciality in UK hospitals showed that compared to other specialties gastroenterologists had the highest utilisation of infliximab biosimilars (14%) in 2015 rising to (62%) by 2016. Followed by rheumatologists 6% to 39%. By contrast, dermatologists had the lowest utilisation of infliximab biosimilars (6%) in 2015 and (35%) in 2016. Diabetologists' utilisation of insulin glargine biosimilar (0.5%) in 2015 and (9%) in 2016 were the least in comparison with the utilisation of infliximab biosimilars by HCPs (Figure 4).

Perception of safety and efficacy
The majority of gastroenterology consultants had no or minor concerns about the safety (95%) (Figure 5A) and efficacy (90%) (Figure 5B) of biosimilars when initiating treatment or when switching patients (95%) (Figure 5C), (93%) (Figure 5D) respectively. Similarly, a large proportion of rheumatology consultants also had no or minor concerns about safety and efficacy when initiating treatment (92%) (Figure 5A), (88%) (Figure 5B) respectively. In contrast, rheumatologists had major concerns about safety (53%) (Figure 5C) and efficacy (55%) (Figure 5D) when switching patients although these reasons only prevented a small proportion from switching patients (2% on safety) and (9% on efficacy) (Figure 5C and D).

Factors increasing the use of biosimilars
Respondents weighted National Institute for Health and Care Excellence (NICE) guidance and robust pharmacovigilance studies on biosimilars equally likely to increase their use of biosimilars. Factors such as local policy, potential cost saving to their organisation and robust cost-effectiveness data for biosimilars versus branded biosimilar medicines were only marginally less important. Cost saving to the respondents' organisation influenced prescribing whether or not these savings were invested in the prescribers' department (Figure 6).

Discussion
Most of UK HCPs that responded (72%) understood correctly what biosimilars were. A minority thought they were new biologics (1%) or generics (18%) and only 6% did not know what biosimilars were (Table 2). Our result show that UK HCPs have a comparable level of knowledge about biosimilars to US specialty physicians and a higher level in comparison with Canadian and French rheumatologists and Ukrainian physicians.[11, 12, 14, 19] Despite this high level of understanding, early prescribing trends of infliximab biosimilars (November, 2015) in the UK showed that they were being prescribed in only 45% of Acute Trusts with a varied degree of uptake among these Trusts.[21] Our results show infliximab biosimilar usage in NHS hospitals rose from 11% in 2015 to

55% in 2016 (Figure 4). This considerable increase most likely reflects the views of the majority of HCPs in our study who considered biosimilars prescribing as important for saving costs to the NHS. Given the existing financial pressures within the NHS this is likely to be a potent driver of prescribing. This is in line with Beck's et al findings in 2016 that 71% of French rheumatologists strongly agreed that biosimilars saved costs for their health services.[14] This financial driver is also implicit in our findings that HCPs held the view that biosimilars are important to stimulate competition in the biological medicine market, since cost competition may lead to downward pressure on prices thus saving costs.[22]

Our survey highlighted a variance in acceptance and utilisation of infliximab biosimilars between specialties, with gastroenterologists the most positive followed by rheumatologists and dermatologists the least accepting (Figures 3 and 4). This is not surprising since gastroenterologists were the highest users of infliximab, whereas rheumatologists use more other biologics and etanercept biosimilar had only just been marketed. Furthermore, published guidance from the British Society of Gastroenterology supported both initiation and switching to biosimilar infliximab whereas the rheumatology and dermatology professional associations were more cautious as discussed later.[23-25] Our findings are in line with the result of a survey of the American Gastroenterological Association in 2015, which found that 72% of gastroenterologists were likely to prescribe biosimilars.[26]

The European Medicine Agency biosimilar approval process involves comparison of the safety and efficacy profiles of biosimilars to their reference biological product.[27] Nonetheless, HCPs' own perception of the safety and efficacy of biosimilars influenced whether they considered starting a new patient or switching a patient to a biosimilar.[28] Our survey showed that gastroenterologist consultants have less concerns about safety and efficacy during initiating and switching to biosimilars than other specialties (Figure 5), which is in line with the European Crohn's Colitis Organisation survey in 2016 that showed that only a minority of inflammatory bowel disease specialists felt little or no confidence in the use of biosimilars.[29]

Whilst rheumatology consultants were similarly less concerned about efficacy and safety in infliximab naïve patients (Figure 5), they expressed more major concerns than other specialties when switching patients from a branded biologic medicine to a biosimilar which may reflect their lower use of infliximab. This cautious approach is also evident in the European League Against Rheumatism report (2016) which stated that patients who develop antibodies against Remicade® were less likely to benefit from infliximab biosimilars and not suitable for switching. Furthermore, published guidance from the British Society for Rheumatology supports the initiation new patients on biosimilars, but recommends the decision to switch patients from originator product to a biosimilar should be on a case-by-case basis until further data are available to support safe switching.[30, 24] Interestingly our study found that safety and efficacy concerns only prevented a small proportion of rheumatologists from switching patients to biosimilars 2% and 9% respectively.

Whilst the British association of dermatology supports the initiation of new patients on biosimilars but not switching responsive patients to alternatives, our results show only slight differences in dermatologists' opinions of using biosimilars in biologic naïve patients or switching. This lack of difference in attitude in our survey findings may reflect the fact that dermatologists were relatively low users of biologics compared to other specialties.[25]

A survey of French rheumatologists in 2016 showed (88%) were prepared to prescribe biosimilars to biologic naïve patient,[14] whereas a survey of European rheumatologists in 2013 showed only 50% likely to prescribe biosimilars.[10] Canadian rheumatologists are even more cautious than their European counterparts stating they were very unlikely or unlikely to prescribe a biosimilars to a biologic naïve patient.[12] This variability in approach to biosimilars may be due to the fact that the surveys were conducted before and after the introduction of these biosimilars (Figure 1). Interestingly a survey among US, France and Germany specialty physicians in 2013, showed that diabetologists/endocrinologists were the least likely to prescribe biosimilars which is similar to our results.[31] Interestingly, the professional associations for this group have yet to issue any guidance on the use of biosimilars.

Our survey suggests that HCPs attitude toward biosimilars may change with the publication of more robust pharmacovigilance studies on biosimilars similarity and guidance from trusted and reputable bodies such as NICE, which is similar to the results of other studies.[16,19] Our results also suggest that reinvesting potential savings in local organisations would encourage the uptake of biosimilars also mirrors the results of the European studies.[14, 32] In view of these responses, a repetition of this survey is needed in the next 1-2 years' time to compare these attitudes following more utilisation of these biosimilars and more publications on switching.

The strength of this study was that we were able to compare and contrast HCPs' attitude toward biosimilars with actual utilisation data. Our study has some limitations. The responses from the professional associations were variable and most of the respondents were consultants/registrars. Only consultants'/registrars' data was used to

interpret safety and efficacy concerns (Figures 3 and 4) to prevent the results being skewed by non-prescribing health care professionals (it is not possible to elicit from the survey whether or not pharmacists and nurses were prescribers). Unfortunately, it was not possible to calculate the response rate as the total number of members of the professional associations and societies are confidential and some HCPs were registered in more than one association or society. Although the number of HCPs in the specialties covered by the survey were not published anywhere, we would estimate that our response rate was low at around 10%, which is a limitation.

Conclusion

UK HCPs have a good understanding of biosimilars and consider biosimilars important as a cost saving measure. There is significant variation between specialties in their attitude to using biosimilars which is also reflected in actual utilisation data. Gastroenterologists and rheumatologists are more likely to initiate a biosimilar than other specialties but rheumatologists have more concerns than gastroenterologists when switching patients. Despite both groups claiming to be influenced by national guidance from NICE, it is probable that personal experience of the specific biologic as well as discipline specific guidance influenced their responses.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors: All authors have contributed to this study and all authors reviewed and approved the final version of the manuscript. SRC designed the study, interpreted the results and reviewed the manuscript and corrected the final version of the manuscript. RWF participated in the study design, interpreted the results and reviewed the manuscript and corrected 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.

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Access to data: All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval: This study approved by the Independent Peer Review Committee at Keele University (Reference 421).

Data sharing statement: Data collected from survey is anonymised. The raw data from which result paper are derived can be made available on request.

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Figure 1 Publication dates of surveys on infliximab and insulin glargine biosimilars

Figure 2 Respondents were asked "how important are the following factors when considering prescribing a biosimilar?"

Figure 3 Respondents (consultants) were asked "how often do you prescribe biosimilars?"

Figure 4 Branded and biosimilar infliximab and insulin glargine utilisation by speciality in UK hospitals between 2015 and 2016

* Reference biological medicine: includes infliximab in dermatology, gastroenterology and rheumatology speciality and insulin glargine in diabetology speciality

**Biosimilar(s): includes infliximab biosimilars (Inflectra and Remsima)® and insulin glargine biosimilar (Abasaglar)®, (Flixabi® and Lusduna® were not included as they have not been used yet in the UK).

Figure 5 Respondents (consultants) were asked "how concerned are you about safety and efficacy when considering starting or switching to biosimilars?"

A: Starting new patients - Safety concerns. B: Starting new patients - Efficacy concerns. C: Switching patients - Safety concerns. D: Switching patients - Efficacy concerns.

Figure 6 Respondents were asked "How likely are the following factors to increase your use of biosimilars?"

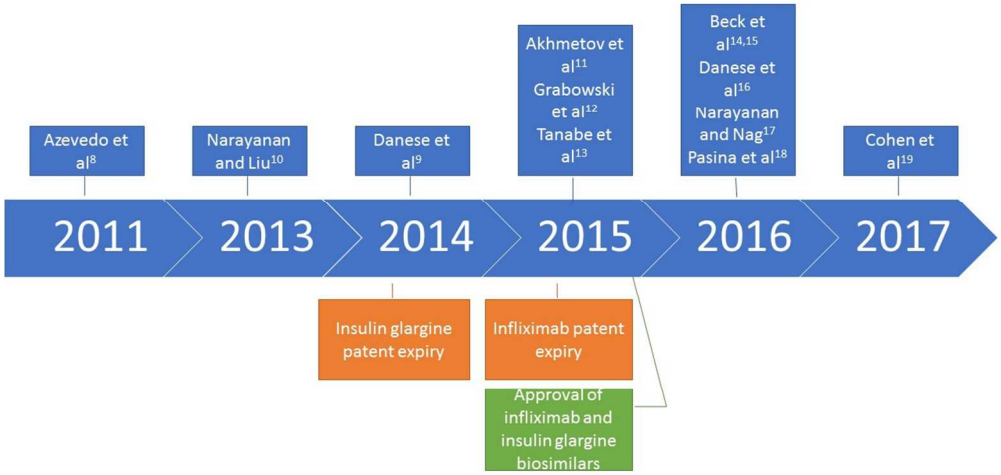

Figure 1 Publication dates of surveys on infliximab and insulin glargine biosimilars

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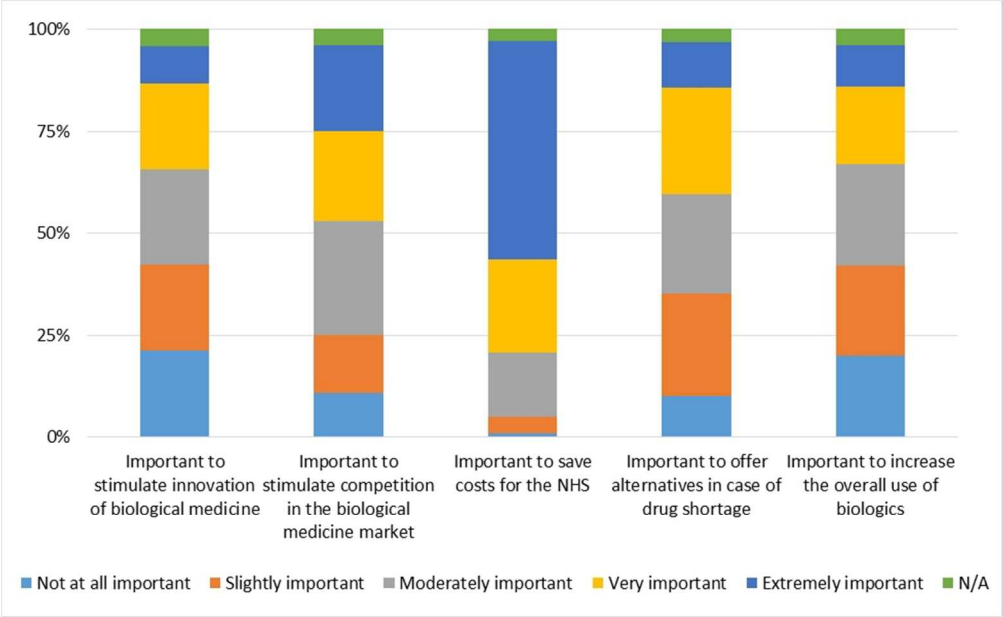

Figure 2 Respondents were asked "how important are the following factors when considering prescribing a biosimilar?"

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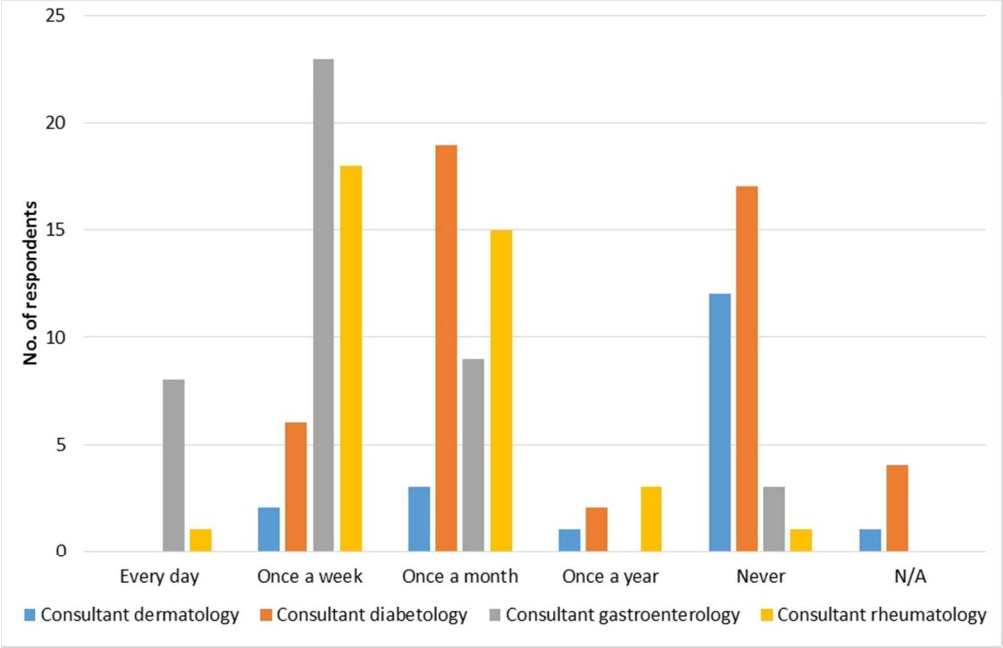

Figure 3 Respondents (consultants) were asked "how often do you prescribe biosimilars?"

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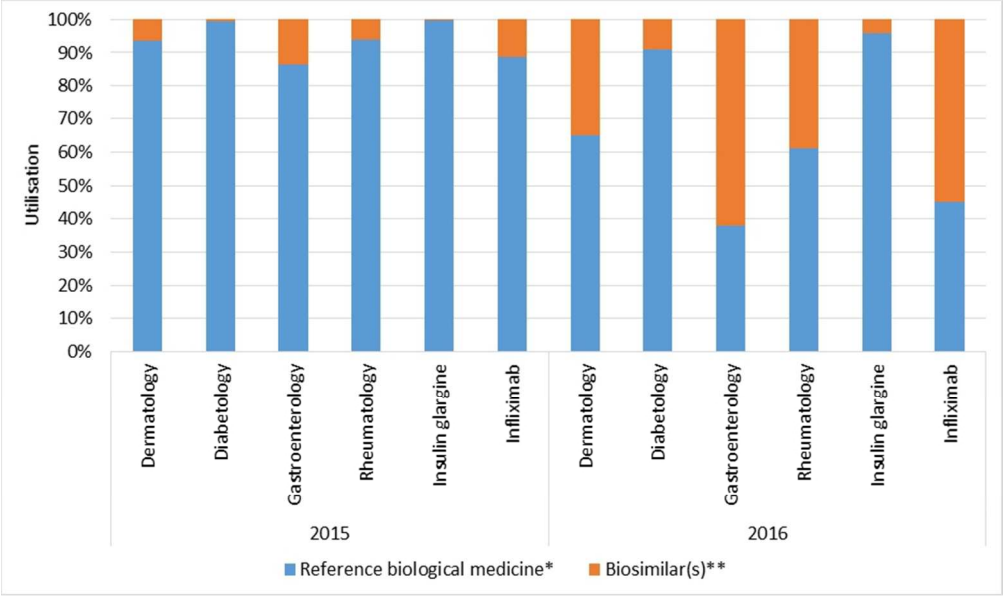

Figure 4 Branded and biosimilar infliximab and insulin glargine utilisation by speciality in UK hospitals between 2015 and 2016

* Reference biological medicine: includes infliximab in dermatology, gastroenterology and rheumatology speciality and insulin glargine in diabetology speciality

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78x46mm (300 x 300 DPI)

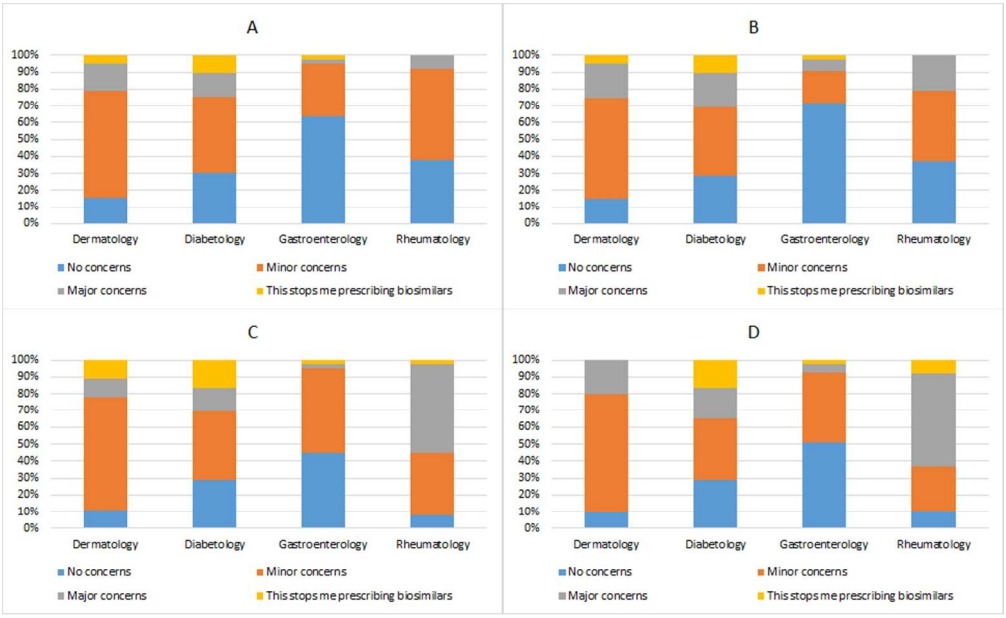

Figure 5 Respondents (consultants) were asked "how concerned are you about safety and efficacy when considering starting or switching to biosimilars?"
A: Starting new patients - Safety concerns. B: Starting new patients - Efficacy concerns. C: Switching patients - Safety concerns. D: Switching patients - Efficacy concerns.

132x80mm (300 x 300 DPI)

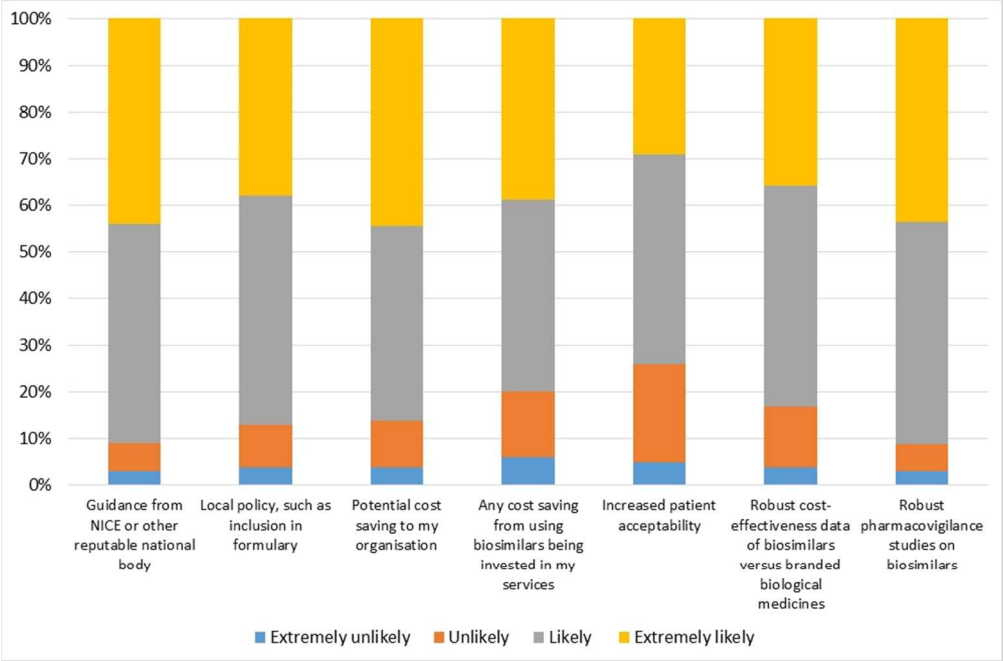

Figure 6 Respondents were asked "How likely are the following factors to increase your use of biosimilars?"

84x55mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Page No	Recommendation
Title and abstract	1	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2	3	Explain the scientific background and rationale for the investigation being reported
Objectives	3	3	State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	3	Present key elements of study design early in the paper
Setting	5	3	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	3	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	3-4	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	*3-4*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9		Describe any efforts to address potential sources of bias
Study size	10		Explain how the study size was arrived at
Quantitative variables	11	4	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	4	(*a*) Describe all statistical methods, including those used to control for confounding
		4	(*b*) Describe any methods used to examine subgroups and interactions
			(*c*) Explain how missing data were addressed
			(*d*) If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses
Results			
Participants	13*	4	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		7	(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
Descriptive data	14*	4	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
			(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	4-5	Report numbers of outcome events or summary measures
Main results	16		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

			(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	5	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	5	Summarise key results with reference to study objectives
Limitations	19	6-7	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	5-6	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	6-7	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22	7	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: Result of a UK web-based survey

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Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: Result of a UK web-based survey

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WORD COUNT: 2549

Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: Result of a UK web-based survey

Abstract

Objective: To investigate health care professionals' knowledge and attitudes towards infliximab and insulin glargine biosimilars and the factors influencing their prescribing. Then, to compare health care professionals' attitudes with the utilisation of these biosimilars in UK hospitals.

Design: Self-administered, one-time web-based survey and drug utilisation analysis.

Setting and data sources: Professional associations and societies in the field of dermatology, diabetology, gastroenterology and rheumatology in the UK, between 8th of August 2016 to 8th of January 2017. The volume of utilisation of branded and biosimilar infliximab and insulin glargine in UK hospitals was derived from the DEFINE database, between 2015 and 2016.

Outcomes: Participants' knowledge and awareness of biosimilars and factors influencing their use and corresponding usage of infliximab and insulin glargine biosimilars.

Results: Responses were obtained from 234 healthcare professionals across dermatology, diabetology, gastroenterology and rheumatology specialties. 75% of respondents were aware that biosimilars were available on their local formulary. 77% of respondents considered biosimilars extremely or very important to save costs for the NHS. Gastroenterologists had the highest utilisation of infliximab biosimilars (14%) in 2015 rising to (62%) in 2016. Healthcare professionals had greater concerns about safety and efficacy when switching patients to biosimilars than when starting biosimilars in biologic naïve patients. Guidance from NICE and robust pharmacovigilance studies on biosimilars were both considered important factors in increasing biosimilars use.

Conclusion: British healthcare professionals are well informed about biosimilars with high level of awareness. Safety and efficacy concerns were higher in switching than in initiating biosimilars among some prescribers. It is probable that personal experience of biologics as well as discipline specific guidance influenced prescribers' responses.

Strengths and limitations of study

- *Respondents were members of professional associations in gastroenterology, rheumatology, dermatology and diabetology in UK so were judged to be representative of the discipline. There were no financial incentives or inducements to complete the survey.*
- *Opinions surveyed were those of prescribing consultants only which potentially could lead to bias, but we believe this unlikely as there are no advantage or disadvantages to the individual as a result of negative or positive results to the survey. It was not possible to calculate the response rate from the professional association as the details of members and size of membership is confidential.*
- *Analyses of national utilisation produced results which reflected the qualitative opinions of the discipline surveyed, implying that the opinions surveyed were representative and generalisable.*

Introduction

Biosimilars are a non-branded copy of approved and patent expired biological medicines.[1] The emergence of biosimilars means these less expensive biological medicines have the potential to produce cost savings for the NHS.[2] Since 2006, 28 biosimilars (corresponding to 11 active molecules) have been licensed in Europe, but the uptake of biosimilars has varied between countries.[3, 4] It is possible that a variance in understanding amongst healthcare prescribers of the potential risks and benefits surrounding biosimilars may account for this varied uptake.[5] With the recent marketing (2015-2017) of biosimilar "blockbuster drugs" such as infliximab, insulin glargine, etanercept and rituximab, and the European Medicine Agency approval of adalimumab biosimilars (patent expiration in 2018) and the subsequent potentially large cost savings to health systems, there has been an increased focus on this area of prescribing.[3, 6] Thus, all health care professionals (HCPs) are likely to encounter patients for whom a biosimilar has been, or could be prescribed.[7]

The variance in uptake of biosimilars suggests that despite a wealth of clinical and scientific literature, regulatory documents, and expert opinion on early approved biosimilars (somatropin, epoetin and filgrastim), HCPs may still have some reservations about using these medicines and more recent biosimilars (infliximab and insulin glargine) in which clinical and non clinal studies on switching originator to biosimilar are required.

A survey of the literature revealed only 12 studies on HCPs knowledge and understanding on infliximab and insulin glargine biosimilars before and after their introduction (Figure 1), and no previous study conducted among HCPs in the UK, which is considered a relatively large market for biological and generic medicines and a potentially attractive market for the biosimilars.[8-19] Only three out of the 12 available studies were conducted in Europe. Narayanan and Liu (2013) and Narayanan and Nag (2016),[10, 17] focused on the likelihood of use of biosimilars among rheumatologists, while, Danese et al., (2016) focused on the change in knowledge of biosimilar among inflammatory bowel disease specialists. None of the retrieved studies focused or compared HCPs concerns about safety and efficacy when considering starting biosimilars or switching patients to biosimilars.[16] To fill this gap in knowledge this study aimed to explore UK HCPs' knowledge, attitudes and practice towards biosimilars in general and compare and contrast the results with the utilisation of infliximab and insulin glargine biosimilars in hospitals in UK.

Methods

Survey design

This was a non-interventional, anonymised, self-administered, one-time web-based survey among HCPs in the UK. This survey was conducted over five months, from 8th of August 2016 to 8th of January 2017. This study approved by the Independent Peer Review Committee at Keele University.

Survey sample

Specialists (consultants, registrars, pharmacists and nurses) in dermatology, diabetology, gastroenterology and rheumatology who were registered members of the British Society of Gastroenterology, the British Society of Paediatric Gastroenterology Hepatology and Nutrition, the Welsh Association for Gastroenterology & Endoscopy, the British Society for Medical Dermatology, the British Society for Paediatric Endocrinology and Diabetes, the Association of British Clinical Diabetologists, the British Dermatological Nursing Group, the Scottish Society for Rheumatology, the British Society for Rheumatology.

Survey procedure

The survey was a closed survey. A request to distribute an invitation to participate in this web-survey was emailed to the professional associations and societies. The invitation letter included a link to the web survey. Reminder emails were sent via the professional associations at four weeks after the initial mailing. The survey front page includes information, describing the survey and asking for their voluntary participation. By reading and responding they gave their consent. The survey questionnaires were designed in such a way that it could not be submitted until all questions had been answered. All the respondents were able to review and change their responses by scrolling up and down the page before submission. Cookies were used by the survey tool allowing only one response per computer. The survey tool was designed to allow only fully completed questionnaires to be submitted for analysis.

Survey questionnaire

An 11-question questionnaire was developed from emerging themes in the current literature on biosimilars and designed using an electronic website (Survey Monkey). The EBSCOhost online research database and PubMed online research database were searched using the terms healthcare professional, physician, doctor, clinician, consultant, registrar, general practitioner, pharmacist, nurse, rheumatologist, gastroenterologist, endocrinologist, diabetologist, dermatologist, survey, web-survey, knowledge, attitude, awareness, perception, opinion, experience, behaviour, practice, biosimilar, subsequent entry biologic and me too biologic. Questions were

developed to investigate knowledge, experience and opinions towards biosimilars. The survey was piloted on a small number of HCPs and revised appropriately to eliminate redundancy and difficult or ambiguous questions. Questionnaires were not asking any personally identifying information.

Utilisation data

Data on infliximab and insulin glargine utilisation by speciality in UK hospitals were taken from DEFINE Software since the introduction of infliximab and insulin glargine biosimilars in March and September 2015 respectively to December 2016. The DEFINE Software is a NHS prescribing database of medicines usage which collects data from approximately 120 hospitals who subscribe to the software package (covering over 90% of NHS hospitals throughout the UK including Specialist Centres and Mental Health Trusts). [20]

Statistical analysis

The survey responses to individual questions were collected, summarised as number and percentage of responding HCPs using Survey Monkey and Microsoft Excel 2013. The percentage of infliximab and insulin glargine biosimilars uptake was calculated using Microsoft Excel 2013.

Results

Characterisation of participants

A total of 234 HCPs participated in the survey and responses were relatively evenly distributed between the various specialities. The majority of responses (64%) (n=150) were from consultants and registrars. Most of the survey participants 64% (n=150) were general hospital based HCPs, followed by tertiary centre based HCPs 30% (n=70), while the remaining were primary care based or in other settings 6% (n=14) (Table 1).

Table 1 Characteristics of participants

Characteristics		Percentage	Number
Profession	Consultants and registrars	64%	150
	Pharmacists	11%	26
	Nurses	25%	58
Speciality	Dermatology	26%	61
	Diabetology	25%	58
	Gastroenterology	23%	54
	Rheumatology	26%	61
Work setting	Primary care	4%	9
	General hospitals	64%	150
	Tertiary centres	30%	70
	Other settings	2%	5

Knowledge and awareness of biosimilars

Most survey participants (72%) thought biosimilars were similar copies of biological medicines, 18% thought they were generic biological medicines, 1% had thought they were new biological medicines and 3% thought they were counterfeit medicines. A minority (3%) stated that they had heard about biosimilars but did not know what they were, and 3% had never heard about biosimilars. A large proportion of the respondents (75%) were aware that biosimilars were available on their local formulary (Table 2).

Table 2 participants' knowledge and awareness

Question	Answer	Percentage	Number

Which statement best describes what you understand a biosimilar to be…	A similar copy of a biological medicine	72%	168
	A generic biological medicine	18%	42
	A counterfeit copy of a biological medicine	3%	6
	A new biological medicine	1%	3
	I have heard about biosimilars but I do not know what they are	3%	8
	I have never heard about biosimilars	3%	7
Are biosimilars on your local formulary?	Yes	75%	174
	No	9%	21
	I do not know	15%	36
	Not applicable	1%	2

Importance of biosimilars prescribing
Cost saving was the dominant consideration when prescribing biosimilars (Figure 2).

Frequency of prescribing biosimilars
Gastroenterology consultants were the most frequent prescribers of biosimilars (prescribing biosimilars every day or week), followed by rheumatologists and diabetologists. Dermatologists prescribed biosimilars the least frequently (Figure 3).

Utilisation of infliximab and insulin glargine
Analysis of the utilisation of infliximab by speciality in UK showed that compared to other specialties gastroenterologists had the highest utilisation of infliximab (67%), followed by rheumatologists (27%) and dermatologists (6%). Further Analysis of the utilisation of branded and biosimilar infliximab and insulin glargine by speciality in UK hospitals showed that compared to other specialties gastroenterologists had the highest utilisation of infliximab biosimilars (14%) in 2015 rising to (62%) by 2016. Followed by rheumatologists 6% to 39%. By contrast, dermatologists had the lowest utilisation of infliximab biosimilars (6%) in 2015 and (35%) in 2016. Diabetologists' utilisation of insulin glargine biosimilar (0.5%) in 2015 and (9%) in 2016 were the least in comparison with the utilisation of infliximab biosimilars by HCPs (Figure 4).

Perception of safety and efficacy
The majority of gastroenterology consultants had no or minor concerns about the safety (95%) (Figure 5A) and efficacy (90%) (Figure 5B) of biosimilars when initiating treatment or when switching patients (95%) (Figure 5C), (93%) (Figure 5D) respectively. Similarly, a large proportion of rheumatology consultants also had no or minor concerns about safety and efficacy when initiating treatment (92%) (Figure 5A), (88%) (Figure 5B) respectively. In contrast, rheumatologists had major concerns about safety (53%) (Figure 5C) and efficacy (55%) (Figure 5D) when switching patients although these reasons only prevented a small proportion from switching patients (2% on safety) and (9% on efficacy) (Figure 5C and D).

Factors increasing the use of biosimilars
Respondents weighted National Institute for Health and Care Excellence (NICE) guidance and robust pharmacovigilance studies on biosimilars equally likely to increase their use of biosimilars. Factors such as local policy, potential cost saving to their organisation and robust cost-effectiveness data for biosimilars versus branded biosimilar medicines were only marginally less important. Cost saving to the respondents' organisation influenced prescribing whether or not these savings were invested in the prescribers' department (Figure 6).

Discussion
Most of UK HCPs that responded (72%) understood correctly what biosimilars were. A minority thought they were new biologics (1%) or generics (18%) and only 6% did not know what biosimilars were (Table 2). Our result show that UK HCPs have a comparable level of knowledge about biosimilars to US specialty physicians and a higher level in comparison with Canadian and French rheumatologists and Ukrainian physicians.[11, 12, 14, 19] Despite this high level of understanding, early prescribing trends of infliximab biosimilars (November, 2015) in

the UK showed that they were being prescribed in only 45% of Acute Trusts with a varied degree of uptake among these Trusts.[21] Our results show infliximab biosimilar usage in NHS hospitals rose from 11% in 2015 to 55% in 2016 (Figure 4). This considerable increase most likely reflects the views of the majority of HCPs in our study who considered biosimilars prescribing as important for saving costs to the NHS. Given the existing financial pressures within the NHS this is likely to be a potent driver of prescribing. This is in line with Beck's et al findings in 2016 that 71% of French rheumatologists strongly agreed that biosimilars saved costs for their health services.[14] This financial driver is also implicit in our findings that HCPs held the view that biosimilars are important to stimulate competition in the biological medicine market, since cost competition may lead to downward pressure on prices thus saving costs.[22]

Our survey highlighted a variance in acceptance and utilisation of infliximab biosimilars between specialties, with gastroenterologists the most positive followed by rheumatologists and dermatologists the least accepting (Figures 3 and 4). This is not surprising since gastroenterologists were the highest users of infliximab, whereas rheumatologists use more other biologics and etanercept biosimilar had only just been marketed. Furthermore, published guidance from the British Society of Gastroenterology supported both initiation and switching to biosimilar infliximab whereas the rheumatology and dermatology professional associations were more cautious as discussed later.[23-25] Our findings are in line with the result of a survey of the American Gastroenterological Association in 2015, which found that 72% of gastroenterologists were likely to prescribe biosimilars.[26]

The European Medicine Agency biosimilar approval process involves comparison of the safety and efficacy profiles of biosimilars to their reference biological product.[27] Nonetheless, HCPs' own perception of the safety and efficacy of biosimilars influenced whether they considered starting a new patient or switching a patient to a biosimilar.[28] Our survey showed that gastroenterologist consultants have less concerns about safety and efficacy during initiating and switching to biosimilars than other specialties (Figure 5), which is in line with the European Crohn's Colitis Organisation survey in 2016 that showed that only a minority of inflammatory bowel disease specialists felt little or no confidence in the use of biosimilars.[29]

Whilst rheumatology consultants were similarly less concerned about efficacy and safety in infliximab naïve patients (Figure 5), they expressed more major concerns than other specialties when switching patients from a branded biologic medicine to a biosimilar which may reflect their lower use of infliximab. This cautious approach is also evident in the European League Against Rheumatism report (2016) which stated that patients who develop antibodies against Remicade® were less likely to benefit from infliximab biosimilars and not suitable for switching. Furthermore, published guidance from the British Society for Rheumatology supports the initiation of new patients on biosimilars, but recommends the decision to switch patients from originator product to a biosimilar should be on a case-by-case basis until further data are available to support safe switching.[30, 24] Interestingly our study found that safety and efficacy concerns only prevented a small proportion of rheumatologists from switching patients to biosimilars 2% and 9% respectively.

Whilst the British association of dermatology supports the initiation of new patients on biosimilars but not switching responsive patients to alternatives, our results show only slight differences in dermatologists' opinions of using biosimilars in biologic naïve patients or switching. This lack of difference in attitude in our survey findings may reflect the fact that dermatologists were relatively low users of biologics compared to other specialties.[25]

A survey of French rheumatologists in 2016 showed (88%) were prepared to prescribe biosimilars to biologic naïve patient,[14] whereas a survey of European rheumatologists in 2013 showed only 50% likely to prescribe biosimilars.[10] Canadian rheumatologists are even more cautious than their European counterparts stating they were very unlikely or unlikely to prescribe a biosimilars to a biologic naïve patient.[12] This variability in approach to biosimilars may be due to the fact that the surveys were conducted before and after the introduction of these biosimilars (Figure 1). Interestingly a survey among US, France and Germany specialty physicians in 2013, showed that diabetologists/endocrinologists were the least likely to prescribe biosimilars which is similar to our results.[31] Interestingly, the professional associations for this group have yet to issue any guidance on the use of biosimilars.

Our survey suggests that HCPs attitude toward biosimilars may change with the publication of more robust pharmacovigilance studies on biosimilars similarity and guidance from trusted and reputable bodies such as NICE, which is similar to the results of other studies.[16,19] Our results also suggest that reinvesting potential savings in local organisations would encourage the uptake of biosimilars also mirrors the results of the European studies.[14, 32] Since the British and European professional associations are intertwined and share a similar position toward biosimilars (such as the British society of rheumatology and the EULAR), and the unique biosimilars approval process by the European medicine agency, it is expected that the findings of our survey could be applied to other health systems in Europe or other health systems with similar guidelines.

In view of these responses, a repetition of this survey is needed in the next 1-2 years' time to compare these attitudes following more utilisation of these biosimilars and more publications on switching.

The strength of this study was that we were able to compare and contrast HCPs' attitude toward biosimilars with actual utilisation data. Our study has some limitations. The responses from the professional associations were variable and most of the respondents were consultants/registrars. Only consultants'/registrars' data was used to interpret safety and efficacy concerns (Figures 3 and 4) to prevent the results being skewed by non-prescribing health care professionals (it is not possible to elicit from the survey whether or not pharmacists and nurses were prescribers). Unfortunately, it was not possible to calculate the response rate as the total number of members of the professional associations and societies are confidential and some HCPs were registered in more than one association or society. Although the number of HCPs in the specialties covered by the survey were not published anywhere, we would estimate that our response rate was low at around 10%, which is a limitation.

Conclusion

UK HCPs have a good understanding of biosimilars and consider biosimilars important as a cost saving measure. There is significant variation between specialties in their attitude to using biosimilars which is also reflected in actual utilisation data. Gastroenterologists and rheumatologists are more likely to initiate a biosimilar than other specialties but rheumatologists have more concerns than gastroenterologists when switching patients. Despite both groups claiming to be influenced by national guidance from NICE, it is probable that personal experience of the specific biologic as well as discipline specific guidance influenced their responses.

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Access to data: All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval: This study approved by the Independent Peer Review Committee at Keele University (Reference 421).

Data sharing statement: Data collected from survey is anonymised. The raw data from which result paper are derived can be made available on request.

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Figure 1 Publication dates of surveys on infliximab and insulin glargine biosimilars

Figure 2 Respondents were asked "how important are the following factors when considering prescribing a biosimilar?"

Figure 3 Respondents (consultants) were asked "how often do you prescribe biosimilars?"

Figure 4 Branded and biosimilar infliximab and insulin glargine utilisation by speciality in UK hospitals between 2015 and 2016

* Reference biological medicine: includes infliximab in dermatology, gastroenterology and rheumatology speciality and insulin glargine in diabetology speciality

**Biosimilar(s): includes infliximab biosimilars (Inflectra and Remsima)® and insulin glargine biosimilar (Abasaglar)®, (Flixabi® and Lusduna® were not included as they have not been used yet in the UK).

Figure 5 Respondents (consultants) were asked "how concerned are you about safety and efficacy when considering starting or switching to biosimilars?"

A: Starting new patients - Safety concerns. B: Starting new patients - Efficacy concerns. C: Switching patients - Safety concerns. D: Switching patients - Efficacy concerns.

Figure 6 Respondents were asked "How likely are the following factors to increase your use of biosimilars?"

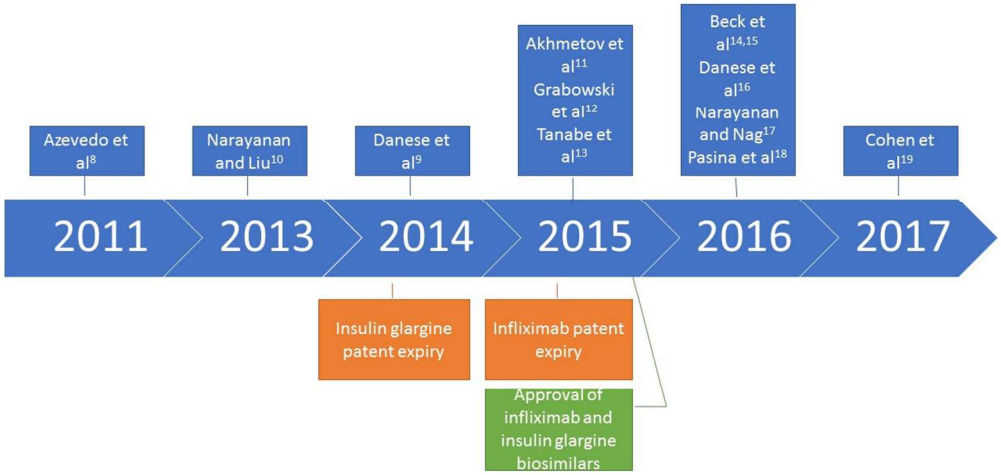

Figure 1 Publication dates of surveys on infliximab and insulin glargine biosimilars

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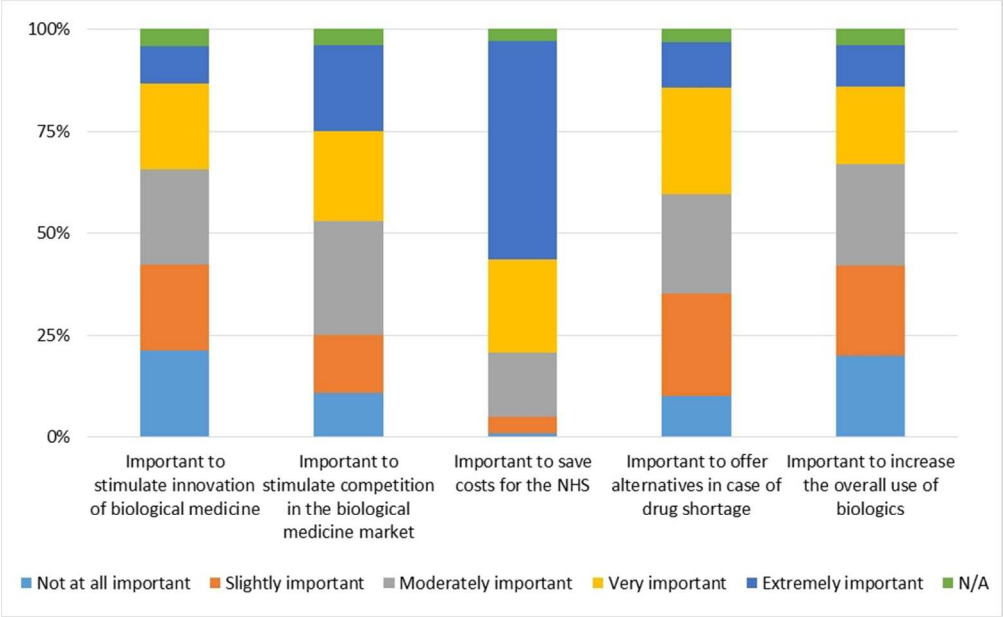

Figure 2 Respondents were asked "how important are the following factors when considering prescribing a biosimilar?"

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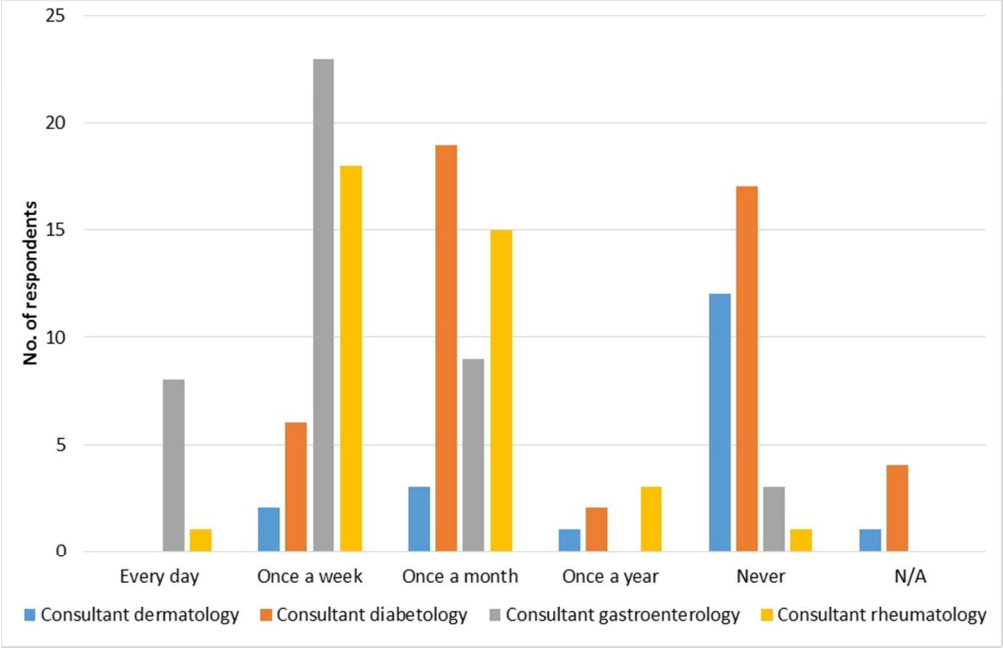

Figure 3 Respondents (consultants) were asked "how often do you prescribe biosimilars?"

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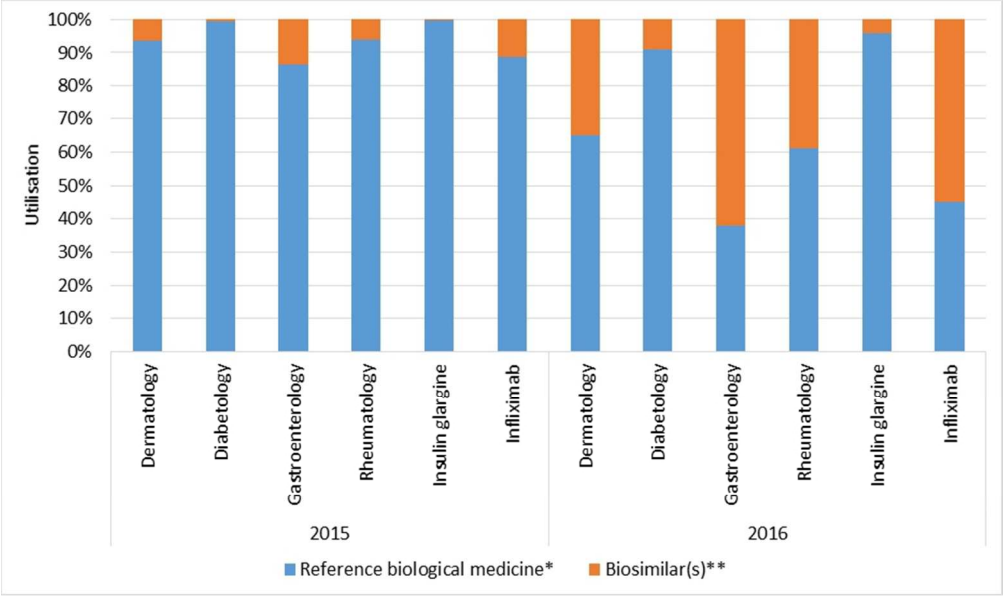

Figure 4 Branded and biosimilar infliximab and insulin glargine utilisation by speciality in UK hospitals between 2015 and 2016

* Reference biological medicine: includes infliximab in dermatology, gastroenterology and rheumatology speciality and insulin glargine in diabetology speciality

**Biosimilar(s): includes infliximab biosimilars (Inflectra and Remsima)® and insulin glargine biosimilar (Abasaglar)®, (Flixabi® and Lusduna® were not included as they have not been used yet in the UK).

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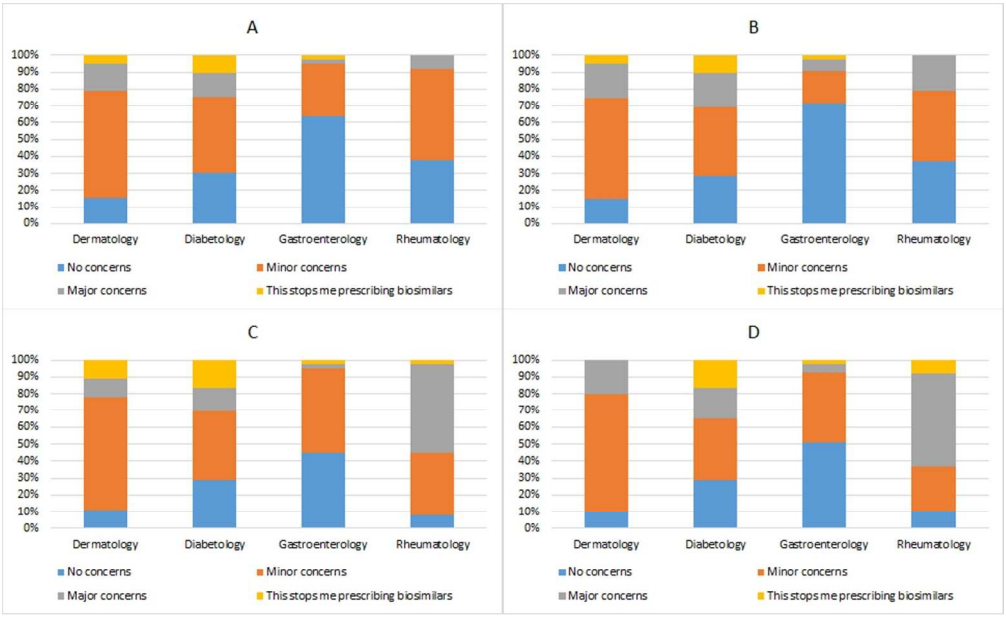

Figure 5 Respondents (consultants) were asked "how concerned are you about safety and efficacy when considering starting or switching to biosimilars?"
A: Starting new patients - Safety concerns. B: Starting new patients - Efficacy concerns. C: Switching patients - Safety concerns. D: Switching patients - Efficacy concerns.

132x80mm (300 x 300 DPI)

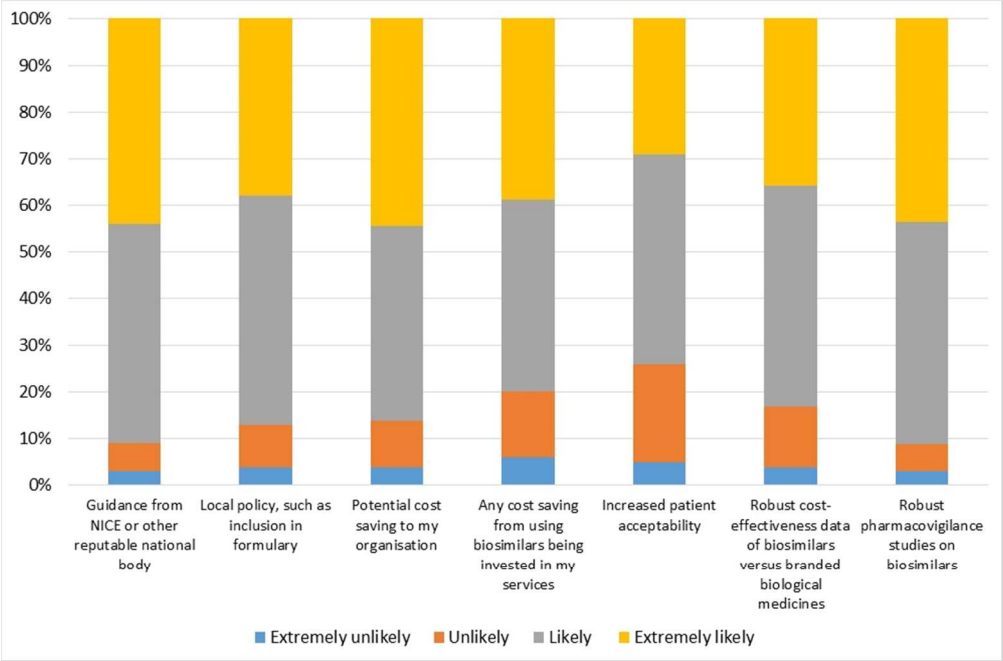

Figure 6 Respondents were asked "How likely are the following factors to increase your use of biosimilars?"

84x55mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract. [Within the title page 1 and method section of the abstract page 2]
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found. [See results section of abstract page 2]
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported. [Page 3, lines 2-23]
Objectives	3	State specific objectives, including any prespecified hypotheses. [Page 3, lines 23-26]
Methods		
Study design	4	Present key elements of study design early in the paper. [Methods page 3]
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection. [Page 3, line 31]
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. [Page 3, line 35-40]
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. [Page 3-4]
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. [Page 3-4]
Bias	9	Describe any efforts to address potential sources of bias. [Strengths and limitations of study page 2, Methods page 3, line 50, Discussion page 7]
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. [Page 4]
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding. [Page 4]
		(*b*) Describe any methods used to examine subgroups and interactions. [Page 4]
		(*c*) Explain how missing data were addressed [Page 3]
		(*d*) If applicable, describe analytical methods taking account of sampling strategy. [N/A]
		(*e*) Describe any sensitivity analyses. [N/A]
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. [Page 4, Table 1]
		(b) Give reasons for non-participation at each stage. [N/A]
		(c) Consider use of a flow diagram. [N/A information in Table 1]
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. [Page 4, Table 1]
		(b) Indicate number of participants with missing data for each variable of

		interest. [N/A]
Outcome data	15*	Report numbers of outcome events or summary measures. [Tables 1 and 2]
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. [N/A]
		(*b*) Report category boundaries when continuous variables were categorized. [N/A]
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. [N/A]
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. [Page 5; Table 2, Figures 2-6]
Discussion		
Key results	18	Summarise key results with reference to study objectives. [Page 5]
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. [Page 7].
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. [Page 5-6]
Generalisability	21	Discuss the generalisability (external validity) of the study results. [Strength and limitation, Page 2; Discussion, Page 6]
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. [Page 7]

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.