PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf)** and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Healthcare professionals' perceptions and perspectives on biosimilar medicines and the barriers and facilitators to their prescribing in UK: a qualitative study
AUTHORS	Aladul, Mohammed Ibrahim; Fitzpatrick, Raymond William; Chapman, Stephen Robert

VERSION 1 – REVIEW

REVIEWER	Professor Keith Petrie University of Auckland, New Zealand
REVIEW RETURNED	28-Apr-2018

GENERAL COMMENTS	This could be an interesting paper but the researchers have used the wrong methodology for the questions they seem to be wanting to answer. The paper uses a qualitative approach which is usually suited to uncovering deeper attitudes, highlighting new areas that have not been considered before in the area or generating new areas of research. However, they use the data they have obtained from 22 HCPs in total and tiny numbers of consultants, pharmacists and nurses when divided by specialty to draw conclusions about wider attitudes. It should be first be acknowledged that each of the HCPs will have a different role in initiating, prescribing and dispensing biosimilars and collapsing these views is unlikely to be appropriate. A more rationale approach would have been to survey a larger sample of these groups separately. The results are presented like it was a quantitative survey "The majority of the HCPs appeared to have a negative opinion...." "About 50% of gastroenterology HCPs.." Actually, that is 3 people. A similar approach is taken throughout the results section. The other criticism is that the paper doesn't really add anything new. This is perhaps because it was analysed as a mini survey rather than a qualitative approach but I suspect there just too few participants with quite different roles in the administering of biologic treatment to be useful.

REVIEWER	Rui Cruz Department of Pharmacy Polytechnic Institute of Coimbra, ESTESC-Coimbra Health School. Portugal.
REVIEW RETURNED	16-May-2018

GENERAL COMMENTS	• Abstract: It is well designed, summarily identifies all parts of the article Suggestion: Page 2, Section Results, Line 1: remove the word… majority… Then the sentence is: “This study showed that the UK healthcare professionals…” • Conclusion: He highlighted the main findings related to the objectives of the research. The less positive aspect is the fact that they do not refer to the limitations of the study itself. • References: Relevant, related and up-to-date; • Suggestion: See reference number 1: the year is 2016: “NICE. Biosimilar medicines: February 2016 update. 2018.”

REVIEWER	Dr Meng-Wong Taing The University of Queensland, Australia
REVIEW RETURNED	13-Jun-2018

GENERAL COMMENTS	This is an interesting and valuable paper that adds to the literature around biosimilar initiation and switching perspectives from different specialist HCP’s. A few points to consider addressing in your manuscript. 1) It is not entirely clear whether all interviewees had prescribing rights. I reviewed the article on the basis that HCPs interviewed are authorised to prescribe. If this is not true, theme titles that include 'prescribing' should be reconsidered and perhaps use terminology such as 'choice/initiation and switching' of biosimilars rather than prescribing. If all HCPs interviewed had prescribing rights, it would be useful to amend lines 39 to – e.g. ‘This included prescribing HCP's’… This will provide clarity to international readers who may are unaware of the prescribing rights of the UK HCPs in the study. e.g. in Australia, only consultants can prescribe biologicals. 2) Table 1: I would prefer more information regarding demographic details of participants e.g. age and working experience (yrs). Did the study reveal any interesting demographic associations with use of biosimilars? Were there any organisational, cultural or hierarchical/power considerations mentioned among interviewees which influenced initiation/switching of biosimilars? 3) It would be useful to highlight the potential cost savings with using biosimilars in the discussion, if this data exists. 4) Pg 9 line 2, write BSG in full. 5) Pg 9 lines 45-end of that section’ regarding choice of reference agent over biosimilar based on price, this viewpoint seems better fitting in potentially ‘Attitudes’ theme. This viewpoint is also repeated on page 11 lines 21-23. Consider consolidating to determine which theme this best fits within.

REVIEWER	João Eurico Fonseca Lisbon Academic Medical Centre
REVIEW RETURNED	14-Jul-2018

GENERAL COMMENTS	In the view of the reviewer 2 methodological details limit the interest of this study. 1-The selection of participants for the interviews appears to be very subjective as it is described in methods. A convenience sampling has generally a method that can be described. Were all HCP with expertise in the field working in the West Midlands hospital invited? Apparently an initial group was approached and then other invitations followed these initial ones in a “snow ball effect”. But this can create a bias in the process. Those who refer other colleagues are likely to be aligned in the same background and opinions. Please be more specific in this methods section. In addition, discuss latter on limitations of this apparently weak strategy of including participants. 2-The other major limitation is already referred in the discussion but in my view it should be better highlighted. Indeed, it is highly likely that those who accepted the interview are already engaged in the use of biosimilars and “aligned” with the questions raised.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Professor Keith Petrie
Institution and Country: University of Auckland, New Zealand
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
This could be an interesting paper but the researchers have used the wrong methodology for the questions they seem to be wanting to answer. The paper uses a qualitative approach which is usually suited to uncovering deeper attitudes, highlighting new areas that have not been considered before in the area or generating new areas of research. However, they use the data they have obtained from 22 HCPs in total and tiny numbers of consultants, pharmacists and nurses when divided by specialty to draw conclusions about wider attitudes. It should be first be acknowledged that each of the HCPs will have a different role in initiating, prescribing and dispensing biosimilars and collapsing these views is unlikely to be appropriate. A more rationale approach would have been to survey a larger sample of these groups separately.

The results are presented like it was a quantitative survey "The majority of the HCPs appeared to have a negative opinion...." "About 50% of gastroenterology HCPs.." Actually, that is 3 people. A similar approach is taken throughout the results section.

The other criticism is that the paper doesn't really add anything new. This is perhaps because it was analysed as a mini survey rather than a qualitative approach but I suspect there just too few participants with quite different roles in the administering of biologic treatment to be useful.

Response to the reviewer: Thank you for your comments. We are aware of the principles of both quantitative and qualitative studies. This work forms part of a broader study, in the first phase of which the authors conducted a web survey among 234 HCPs in UK to investigate HCPs’ knowledge and attitude towards biosimilars and explore the potential factors influencing their prescribing. This is mentioned in the introduction section, Page 3, lines 6-8 but we acknowledge this perhaps justifies greater emphasis and context. This study was intended to explore in greater depth HCPs opinion, attitude and experience towards biosimilars to provide a better understanding of the facilitators and barriers to the uptake of biosimilars in the UK than the initial web survey.

As is usual with qualitative studies, we felt it was the depth of the understanding rather than the number of interviews conducted which adds further insight. The literature indicates that qualitative analyses typically require a smaller sample size than quantitative analyses. There are no specific rules when determining an appropriate sample size in qualitative research. Qualitative sample size may best be determined by the time allotted, resources available, and study objectives (Patton, 1990). Glaser and Strauss (1967) recommend the concept of saturation for achieving an appropriate sample

size in qualitative studies. Creswell (1998) suggests only 20 – 30 for grounded theory approach. And for phenomenological studies, Creswell (1998) recommends five to 25 and Morse (1994) suggests at least six. The authors have analysed the data using thematic analysis, a qualitative approach

As mentioned in the method section in the first paragraph, both nurses and pharmacists interviewed had prescribing rights thus, all the interviews were conducted with HCPs able to prescribe within the British health care system. We accept that pharmacist and nurse roles may differ in other health care systems.

.Reviewer: 2
Reviewer Name: Rui Cruz
Institution and Country: Department of Pharmacy, Polytechnic Institute of Coimbra, ESTESC-Coimbra Health School. Portugal.
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
• Abstract: It is well designed, summarily identifies all parts of the article
Suggestion: Page 2, Section Results, Line 1: remove the word… majority…
Then the sentence is: "This study showed that the UK healthcare professionals…"

Response to the reviewer: Thank you for your comments. This section has been amended.

• Conclusion:
He highlighted the main findings related to the objectives of the research.
The less positive aspect is the fact that they do not refer to the limitations of the study itself.

Response to reviewer: Thank you for your comments. The limitations of the study are stated in the paper highlight section just after the abstract and again in the discussion section.

• References:
Relevant, related and up-to-date;
• Suggestion:
See reference number 1: the year is 2016: "NICE. Biosimilar medicines: February 2016 update. 2018."

Response to the reviewer: This reference has been corrected.

Reviewer: 3
Reviewer Name: Dr Meng-Wong Taing
Institution and Country: The University of Queensland, Australia
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
This is an interesting and valuable paper that adds to the literature around biosimilar initiation and switching perspectives from different specialist HCP's.
A few points to consider addressing in your manuscript.
1) It is not entirely clear whether all interviewees had prescribing rights. I reviewed the article on the basis that HCPs interviewed are authorised to prescribe. If this is not true, theme titles that include 'prescribing' should be reconsidered and perhaps use terminology such as 'choice/initiation and switching' of biosimilars rather than prescribing.
If all HCPs interviewed had prescribing rights, it would be useful to amend lines 39 to – e.g. 'This included prescribing HCP's'…
This will provide clarity to international readers who may are unaware of the prescribing rights of the UK HCPs in the study. e.g. in Australia, only consultants can prescribe biologicals.

Response to the reviewer: Thank you for comment, we totally agree. All the interviewed participants were authorised to prescribe biologics in their speciality. The first paragraph in the method section states that both the nurses and pharmacists were independent prescribers. Having re-visited this, we

accept that this may look confusing for international readers so this paragraph has been amended accordingly.

2) Table 1: I would prefer more information regarding demographic details of participants e.g. age and working experience (yrs). Did the study reveal any interesting demographic associations with use of biosimilars? Were there any organisational, cultural or hierarchical/power considerations mentioned among interviewees which influenced initiation/switching of biosimilars?

Response to the reviewer: Table 1 has been amended to include the age and the years of experience of HCPs. However, due to the small sample size and the diversity of specialities and organisational background, it was not possible to identify a difference in attitude associated with demographics.

3) It would be useful to highlight the potential cost savings with using biosimilars in the discussion, if this data exists.

Response to the reviewer: Thank you for comments –this is a good point. We did, in fact ask the interviewed HCPs about expected cost savings with the utilisation of biosimilar per patient, but, the majority of HCPs answered that prices within secondary care were confidential data and/or that only commissioners, not HCPs have access to these data. In order to demonstrate that we have considered budget impact, we have referenced our recently published article on budget impact analysis relating to the introduction of new anti-TNFs biosimilars and have made reference to this paper in the discussion section.

4) Pg 9 line 2, write BSG in full.

Response to reviewer: This abbreviation has been written in full.

5) Pg 9 lines 45-end of that section' regarding choice of reference agent over biosimilar based on price, this viewpoint seems better fitting in potentially 'Attitudes' theme. This viewpoint is also repeated on page 11 lines 21-23. Consider consolidating to determine which theme this best fits within.

Response to reviewer: That is a good point. This paragraph has been moved to the attitude theme.

Reviewer: 4
Reviewer Name: João Eurico Fonseca
Institution and Country: Lisbon Academic Medical Centre
Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below
In the view of the reviewer 2 methodological details limit the interest of this study.
1-The selection of participants for the interviews appears to be very subjective as it is described in methods. A convenience sampling has generally a method that can be described. Were all HCP with expertise in the field working in the West Midlands hospital invited? Apparently an initial group was approached and then other invitations followed these initial ones in a "snow ball effect". But this can create a bias in the process. Those who refer other colleagues are likely to be aligned in the same background and opinions. Please be more specific in this methods section. In addition, discuss latter on limitations of this apparently weak strategy of including participants.

Response to the reviewer: Thank you for your comments, which we accept. Since this study involved NHS participants, an ethical approval and letter of access first from the NHS Health Research Authority and then from the research and development department in each Trust and hospital within the Trust was needed to conduct the study.
The researcher obtained approval from seven of the 14 acute Trusts within the West Midland area (the University Hospital of North Midlands NHS Trust, the Staffordshire and Stoke on Trent

Partnership NHS Trust, the Royal Wolverhampton NHS Trust, the Heart of England NHS Trust and the University Hospitals Coventry and Warwickshire NHS Trust). We have amended the methodology section explaining the research approval process, as described above.
The researcher invited all diabetology, rheumatology and gastroenterology HCPs (experts in diabetes mellitus, ulcerative colitis, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis where insulin glargine, infliximab and etanercept were prescribed within above mentioned hospitals in the West Midland area by email and/or telephone. Due to the busy life of HCPs and quantity of emails and phone calls received by those HCPs, a snowballing technique was used to get the attention of those HCPs who did not respond to the emails or phone call or to get further names of HCPs who were not listed in the Trust/hospital website.

2-The other major limitation is already referred in the discussion but in my view it should be better highlighted. Indeed, it is highly likely that those who accepted the interview are already engaged in the use of biosimilars and "aligned" with the questions raised.

Response to reviewer: The limitation section has been amended accordingly.

VERSION 2 – REVIEW

REVIEWER	Dr Meng-Wong Taing The University of Queensland, School of Pharmacy. Australia
REVIEW RETURNED	23-Jul-2018

GENERAL COMMENTS	Q) Were there any organisational, cultural or hierarchical/power considerations mentioned among interviewees which influenced initiation/switching of biosimilars? Author response: due to the small sample size and the diversity of specialities and organizational background, it was not possible to identify a difference in attitude associated with demographics. The authors response needs to be included as part of the limitations within the Discussion section of the manuscript. I have no further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name: Dr Meng-Wong Taing
Institution and Country: The University of Queensland, School of Pharmacy. Australia
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Q) Were there any organisational, cultural or hierarchical/power considerations mentioned among interviewees which influenced initiation/switching of biosimilars?

Author response: due to the small sample size and the diversity of specialities and organizational background, it was not possible to identify a difference in attitude associated with demographics.

The authors response needs to be included as part of the limitations within the Discussion section of the manuscript.

Response to the reviewer: Thank you for your notice. This had been added to the limitation section.