

## 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.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Physicians' perceptions of the uptake of biosimilars - A systematic review
<b>AUTHORS</b>	Sarnola, Kati; Merikoski, Merja; Jyrkka, Johanna; Hämeen-Anttila, Katri

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Luis Puig Hospital de la Santa Creu i Sant Pau. Barcelona, Spain
<b>REVIEW RETURNED</b>	30-Sep-2019

<b>GENERAL COMMENTS</b>	<p>This is a state-of-the-art systematic literature review on physicians' perceptions regarding the prescription of similars. In the Discussion, the authors state "Since prescribing decisions are either made by individual physicians or they are steered by policies, it is evident that more binding policies and guidance on prescribing is needed." This can be considered a rather coercive approach, underrating physicians' professionalism and freedom of prescription.</p> <p>Perhaps some more granularity should be added to the current Discussion, including differences across health systems regarding prescription and dispensation of biologics (hospital vs community-based), nature of payers (e.g. National or Local Health Services, HMOs, or Hospitals), degree of copayment, and pricing policies (in some countries a reference price is established by health authorities, which can (e.g. Spain) or cannot (e.g. Romania) be subject to tenders, discounts or bonuses. In some others (e.g. USA), HMOs may have a vested interest in keeping prices high to benefit from under-the-table discounts. These factors might be much more relevant nowadays than physicians' (or patients') perceptions collected before 2017. Incidentally, the differences across medical specialties and the reluctance of oncologists to embrace biosimilars might be the subject of a more detailed analysis.</p>
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<b>REVIEWER</b>	Keith Petrie University of Auckland, NZ
<b>REVIEW RETURNED</b>	21-Oct-2019

<b>GENERAL COMMENTS</b>	This is a timely review of an important area but the authors firstly need to be clear how it is different or improved from the Leonard review published this year [ref 33]
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	<p>The introduction needs some more specific consideration of the importance of physician perceptions towards biosimilars. For example, leading to a reluctance to prescribe biosimilars.</p> <p>The authors should examine whether the understanding and attitudes towards initiating patients on biosimilars/switching varied for different types of physicians.</p> <p>The authors should also consider perceptions towards the interchangeability of biosimilars in the results section.</p> <p>Another important limitation is that studies were conducted in different countries with unique regulatory laws and policies.</p>
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### VERSION 1 – AUTHOR RESPONSE

#### Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Luis Puig

Institution and Country: Hospital de la Santa Creu i Sant Pau. Barcelona, Spain

Please state any competing interests or state 'None declared': Receipt of grants/research supports or participation in clinical trials (paid to Institution) Abbvie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo-Pharma, Lilly, Novartis, Pfizer, Regeneron, Roche, Sanofi, UCB. Receipt of honoraria or consultation fees (paid to myself) Abbvie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, Leo-Pharma, Lilly, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Samsung-Bioepis, Sanofi, UCB.

Participation in a company sponsored speaker's bureau Celgene, Janssen, Lilly, MSD, Novartis, Pfizer;

Stock shareholder None; Other support (please specify) None

This is a state-of-the-art systematic literature review on physicians' perceptions regarding the prescription of similars. In the Discussion, the authors state "Since prescribing decisions are either made by individual physicians or they are steered by policies, it is evident that more binding policies and guidance on prescribing is needed." This can be considered a rather coercive approach, underrating physicians' professionalism and freedom of prescription.

Respectively, we aim, by no means, to underrate physicians' professionalism and their clinical autonomy. At the same time, due to the increasing costs, a more comprehensive need for the uptake of biosimilars has been globally recognised, and thus, steering prescribing patterns may be necessary to handle these increasing medical costs for society in different countries. We have revised the terminology and phrases used in the manuscript accordingly. The sentence referred is now corrected to be: "Prescribing decisions can either be made by individual physicians or, if thereafter necessary, they can be steered by binding policies that vary across countries."

Perhaps some more granularity should be added to the current Discussion, including differences across health systems regarding prescription and dispensation of biologics (hospital vs community-based); nature of payers (e.g. National or Local Health Services, HMOs, or Hospitals), degree of co-payment, and pricing policies (in some countries a reference price is established by health authorities, which can (e.g. Spain) or cannot (e.g. Romania) be subject to tenders, discounts or bonuses. In some others (e.g. USA), HMOs may have a vested interest in keeping prices high to benefit from under-the-table discounts. These factors might be much more relevant nowadays than physicians' (or patients')

perceptions collected before 2017. Incidentally, the differences across medical specialties and the reluctance of oncologists to embrace biosimilars might be the subject of a more detailed analysis. We have revised the Discussion accordingly. A need for further study to explore the differences in the attitudes between disciplines has been added.

Reviewer: 2

Reviewer Name: Keith Petrie

Institution and Country: University of Auckland, NZ

Please state any competing interests or state 'None declared': None declared

This is a timely review of an important area but the authors firstly need to be clear how it is different or improved from the Leonard review published this year [ref 33].

A review by Leonard et al. addresses also other stakeholders but physicians. This review addresses solely the physician perspective on the uptake of biosimilars. Furthermore, in the work by Leonard et al., no quality assessment of included studies was conducted, there was only one reviewer in some parts of the inclusion process and the data was not separately extracted from each study. Therefore, we considered that there was a need for this review. We have added these justifications to the manuscript.

The introduction needs some more specific consideration of the importance of physician perceptions towards biosimilars. For example, leading to a reluctance to prescribe biosimilars. We have revised the Introduction accordingly.

The authors should examine whether the understanding and attitudes towards initiating patients on biosimilars/switching varied for different types of physicians. Understanding and attitudes of physicians with different disciplines (e.g. rheumatology or gastroenterology) are addressed at the end of each section in the Results, if included studies provide some insight to the differences between disciplines. We agree with the reviewer that more comprehensive research on the differences between disciplines in the attitudes towards and prescribing of biosimilars should be conducted in the future. This has been added in the Discussion section.

The authors should also consider perceptions towards the interchangeability of biosimilars in the results section. We have revised the Results section accordingly.

Another important limitation is that studies were conducted in different countries with unique regulatory laws and policies. We agree with the reviewer that included studies were conducted in different countries with unique regulatory laws and policies that undoubtedly effect on the uptake and prescribing of biosimilars in the national level. We have added this limitation to our review. Although this may be considered as a limitation, we consider that it is equally vital to compile studies from different countries with different systems and policies in order to form a comprehensive view on the current situation on the uptake of biosimilars.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Keith Petrie University of Auckland
<b>REVIEW RETURNED</b>	26-Dec-2019

<b>GENERAL COMMENTS</b>	<p>The authors have not addressed how their review is different from the Leonard review published in 2019 apart from a slightly different methodology of extraction and addition of quality rating. In the Leonard review “Studies in English were included if they surveyed U.S. or European physician and/or pharmacist knowledge, attitudes, and/or prescribing preferences of bio- similar drugs. Overall trends in prescribing behavior and perceptions were abstracted”. So how is this review different, why is it needed and what does it add?</p> <p>The current paper seems to include many papers that are included in the previous review and some of those it does not include (e.g. Cassar et al., (2016), Gibofsky et al. (2017), Hallersten (2016), Kellner (2016), Narayanan et al. (2016)) seem to, at least superficially, fit the search criteria.</p> <p>The authors also seem to have included the Leonard systematic review as a publication in their review, which seems bizarre.</p>
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## VERSION 2 – AUTHOR RESPONSE

Reviewer's Comments to Author:

Reviewer: 2

Reviewer Name: Keith Petrie

Institution and Country: University of Auckland, New Zealand Please state any competing interests or state 'None declared': None declared

The authors have not addressed how their review is different from the Leonard review published in 2019 apart from a slightly different methodology of extraction and addition of quality rating. In the Leonard review “Studies in English were included if they surveyed U.S. or European physician and/or pharmacist knowledge, attitudes, and/or prescribing preferences of bio- similar drugs. Overall trends in prescribing behavior and perceptions were abstracted”. So how is this review different, why is it needed and what does it add?

Answer:

Thank you for the critical comment that challenge as explain more clearly the added value of our review. We acknowledge the similarity of our systematic review compared to the Leonard et al. (ref 12 in the current version of our manuscript) review. As answered to Editor's comments, the focus of our aim and literature search, accordingly, was actually wider compared to Leonard et al., even though we focused on physicians perceptions of uptake on biosimilars. We, in fact, ended up with 12 original articles that were not included in the Leonard et al. work. We have added rationale for conducting this systematic review in the introduction-section and acknowledge the work by Leonard et al. now already in the introduction. Furthermore, we compare these two reviews in the Discussion/ Strength and limitations -section.

The current paper seems to include many papers that are included in the previous review and some of those it does not include (e.g. Cassar et al., (2016), Gibofsky et al. (2017), Hallersten (2016), Kellner (2016), Narayanan et al. (2016)) seem to, at least superficially, fit the search criteria.

Answer:

Thank you for pointing us the fact that we have not clearly shown the different inclusion and exclusion criteria of our study compared to Leonard et al. review.

In Leonard et al. review, there were eight studies that were not included in our study. Seven of them did not meet our inclusion criteria (described in table 1 in our manuscript):

- we did not include conference papers (Gibofsky & Badawi 2018, Sidikou et al. 2018, Cassar et al. 2018, Kellner et al. 2018)
- we did not include Letters to Editor (Pasina et al. 2016, Narayanan & Nag 2016)
- at least 45% of participants of the included studies had to be physicians (Dylst et al. 2014: only 2/19 interviewees were physicians)

We have added one study (Hallersten et al. 2016) to our review.

The authors also seem to have included the Leonard systematic review as a publication in their review, which seems bizarre.

Answer:

Following the comments from the Editor and Reviewer, we have excluded Leonard et al. review from the publications included in our review. Due to this unpacking, one study (Hallersten et al. 2016) was added to the publications. Furthermore, we acknowledge Leonard et al. review in the introduction and in the beginning of the discussion, as well as compare these reviews in the Strengths and Limitations -section.