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

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Initial prescriptions and medication switches of biological products: an analysis of prescription pathways and determinants in the Swiss healthcare setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Wirth, Kevin; Boes, Stefan; Näpflin, Markus; Huber, Carola; Blozik, Eva</td>
</tr>
</tbody>
</table>

VERSION 1 – REVIEW

| REVIEWER           | Song, Inmyung  |
|                   | Sungkyunkwan University |
| REVIEW RETURNED   | 26-Aug-2023 |

| GENERAL COMMENTS   | This study produced a very interesting and counterintuitive finding which is that a lower price difference between the reference product and a biosimilar is associated with more prescriptions of the biosimilar. The authors made reasonable efforts to explain the result in terms of the incentive system which could have policy implications. Still, addressing the following comments could improve the paper. |

Background
Some statements need references. One example is “Existing studies have only demonstrated that patients tend to remain on their initial biological treatment product once medication treatment has been initiated.”

Methods
The first paragraph in the Method section is too long. Please cut it in two or more.

(119) Please add more detail on what Pharmaceutical Cost Groups (PCG) are.
(131-132) The categories are not mutually exclusive: (100, 100-599, >600) (10, 10-19, >20)
(143-144) -> All research participants' baseline characteristics are shown as counts and percentages <for categorical variables>, or as mean and standard deviation for continuous variables.

Results
Tables should be self-explanatory. In other words, all numbers described in the text should also appear in the table. For example, the numbers described in the sentence “The study found that a total of 17’654 patients were prescribed at least one biological product, with 56.9% of them (10’046 patients) receiving multiple prescriptions” must also be shown in Table 1.

Table 1
Add data on males
Add the unit, "year", to age group
Add mean age, which is described in the text but not shown in the table
Add the high deductible category

Table 2 also should contain more information. For example, the number ("28.6% were biosimilar prescriptions") is not in Table 2. One way to solve this is to add a row for the combined total for IP and FP.

Discussion
The first paragraph is too long. Please divide it into two or more.
(223-226) The authors compared the share of biosimilars in terms of total prescription (or claims) with that in market sales. This is similar to comparing apples to oranges because the prices of biosimilars are lower than those of reference drugs.

(234) The authors keep using the term “market share”. It appears the authors used the term liberally. To use the term in a traditional sense, the study should have information on the revenue and prices of medication. To avoid confusion, please define the term early on.

In Table A8, by coeff do the authors mean OR? Then use OR instead.

REVIEWER
Shafrin, Jason
FTI Consulting
REVIEW RETURNED
06-Sep-2023

GENERAL COMMENTS
Abstract
• “Helsana, a leading Swiss health insurance”. In what sense is Helsana leading? Is it the most popular private health insurance? I would use a more concrete adjective or remove the term “leading” entirely.
• The abstract does not clarify which patients are included in the analysis. Not all diseases have a biosimilar. Is this only for disease that have an available biosimilar? Please clarify.
• “Increased relative price difference”. This term is not defined. Is this price difference between biologic and biosimilar? Is this measured as absolute difference or % of cost?
• It would be interesting to cite changes in overall biosimilar prescriptions vs. index prescriptions; patients may not want to change medications to a biosimilar if theirs is working, but may be more amendable for new prescriptions.

Background
• In general, the background is good. However, the background should also consider citing other studies that have examined how much biosimilars can reduce prices in different countries. For instance see: Maksabedian Hernandez et al. 2012 (https://www.tandfonline.com/doi/full/10.1080/13696998.2022.2113252)

Methods – Study design and population
• Why is the sample including all people with biologics and biosimilars? It could be the case that many of the biologics have no biosimilars. Thus, if biosimilar uptake was 100%, the study would still find less than 100% uptake since many biologics don’t have biosimilars available. Later (in the measurers section) it says there is a more limited sample for people with biologics available.
• Usually, you don’t report the N’s until the results sections.
• Were patients required to be continuously enrolled for a specific time period to be included in the analysis?

Methods - Measures
• Is the copay observed only if the patient fills the medication? If that is the case, this variable could be biased if people decide not to fill a prescription because the copay is too high. How do the authors take into account this potential bias.
• “comprehensive set of variables characterized the prescribed medications”. I wouldn’t say “comprehensive” since there is always missing information in every data set.

Methods – Statistical Analysis
• “Chi-squared tests 150 were used to determine whether the prevalence was equivalent across the year”. Is this prevalence of biosimilar use among all patients using a biological product or only those where a biosimilar was available? Please be clear.
• “Three different logistic models with different sets of variables were computed (Table A8).” Explain why there were 3 different models.
• “Both, Model B and C, show similar results and a better fit of the estimates compared to Model A based on the goodness-of-fit criteria (AIC, BIC).” Explain what models A, B and C correspond to. Also, do not give results in the methods section.
• It would be interesting to look at the time since biosimilar launch as well as uptake make take some time.

Results
• The results section seems to be limited to people with prescriptions where there is a biosimilar substitute. This makes sense but throughout the methods this is not clear.
• A CONSORT table / CONSORT diagram is needed.
• For Table 1, it seems that this analysis is at the patient-index prescription (IP) level rather than the patient level, because you state that there were “17’654 individuals (or 18’953 IPs, respectively)". Thus, be clear that the table is at the patient-IP level not the patient level. You may want to consider a patient characteristics table where you look at patient characteristics based on first IP so you are not double counting individuals. That would be a useful sensitivity analysis.
• How representative is the study population compared to the general Swiss population?
• “15.1% (2’672 patients) received multiple biosimilars”. Is this multiple biosimilar prescriptions are two different types of drug? Please clarify.
• Wouldn’t the results be impacted by the composition of the drugs. For instance, it could be that biosimilar % rises over time for every reference product. However, as new biosimilars enter, they are then added to your data set at low initial uptake rates. Thus, you may want to re-run the analysis looking at years since biosimilar launch to see if that increases monotonically over time. We do see some increase in biosimilar use in the regression and certainly it is the case that more biosimilars available increase biosimilar usage.
• The large switch between biosimilars to reference products is surprising. It would be useful to discuss why you think this is happening in the discussion.
• “In terms of pharmaceutical variables, monoclonal antibodies, LMW heparins and growth factors were associated with substantially lower biosimilar IP occurrences (-88.5%, -99.9% and -84.2%) than fusion proteins.” Are these percentages or absolute differences. I assume the former but please clarify.
Discussion

• You may want to link the statement “Moreover, the current incentive system discourages the prescription of biosimilars for self-dispensing doctors and pharmacies as they are rewarded for prescribing the more expensive product by a bigger profit margin” to your finding that physicians switch from biosimilar to reference in the data.

• For biosimilars, one would guess that these would work nearly identically to the reference product. However, reimbursement is lower and it could be the case that manufacturing quality is less consistent. If there is evidence of that, it may be useful to cite that; if not feel free to ignore this comment.

• “The strongest barrier for biosimilar prescriptions was the increasing relative price difference between biosimilar and reference product”. Why is this a barrier? The authors state that this is because physicians are unfamiliar with them, but why does price impact this? Is this because physicians consider price to play a signaling role for quality?

• The stockpiling of different medications is a very interesting point. A reason against diversifying to biosimilars if you’d need to store the brand also.

Version 1 – Author Response

Reviewer: 1
Dr. Inmyung Song, Sungkyunkwan University

Comments to the Author:

This study produced a very interesting and counterintuitive finding which is that a lower price difference between the reference product and a biosimilar is associated with more prescriptions of the biosimilar. The authors made reasonable efforts to explain the result in terms of the incentive system which could have policy implications. Still, addressing the following comments could improve the paper.

Background

Some statements need references. One example is “Existing studies have only demonstrated that patients tend to remain on their initial biological treatment product once medication treatment has been initiated.”

Response: We thank the reviewer for the valuable feedback. We have taken your suggestion into account and have now added supporting references to statements in our manuscript, including the one you mentioned.

Methods

The first paragraph in the Method section is too long. Please cut it in two or more.

Response: We appreciate the reviewers comment increasing the manuscripts readability. We shortened the first paragraph (89-98) of the method section and additional parts of the “Measures” section (115-158).

(119) Please add more detail on what Pharmaceutical Cost Groups (PCG) are.

Response: We thank the reviewer and provided further information (including the original study) clarifying shortly the concept of PCGs.

131: “We assessed comorbidity using the number of Pharmaceutical Cost Groups (PCG) per patient (0,1,2,>2). PCGs are a recognized proxy for the presence of chronic diseases using data on
medications bills that were reimbursed [18]."

(131-132) The categories are not mutually exclusive: (100, 100-599, >600) (10, 10-19, >20)
Response: We thank the reviewer for the important notice. We corrected the categories as used in the methods.

(143-144) - All research participants' baseline characteristics are shown as counts and percentages, or as mean and standard deviation for continuous variables.
Response: We kindly request further clarification in order to appropriately integrate this comment into the manuscript.

Results
Tables should be self-explanatory. In other words, all numbers described in the text should also appear in the table. For example, the numbers described in the sentence “The study found that a total of 17'654 patients were prescribed at least one biological product, with 56.9% of them (10'046 patients) receiving multiple prescriptions” must also be shown in Table 1.
Response: We highly value the reviewer’s input. Based on the feedback, we have opted to remove the paragraph (206-210) from this section. The section dedicated to biosimilar switches already provides a more comprehensive exploration of patients with multiple prescriptions. By omitting this paragraph, we believe we can enhance readability without sacrificing important information.

Table 1
Add data on males
Response: We thank the reviewer. We added information on males in Table 1.

Add the unit, “year”, to age group
Response: The reviewers note is greatly appreciated. We supplemented the proposed unit.

Add mean age, which is described in the text but not shown in the table
Response: Thank the reviewer for the valuable feedback. As we used the age categories in the regression model, we decided to stick with those in order to stay consistent throughout the manuscript. As we have already presented age information in Table 1, we have opted not to redundantly insert the age average in Table 1. Instead, we have modified the age-related information in the introduction of the results section, aligning with the suggestion to create self-explanatory tables.

200: “The study’s overall population demonstrated a balanced distribution among age categories (<50, 50-64, 65-74, >74). Notably, individuals prescribed reference products as IP were more prevalent in the highest age group, while those initially prescribed biosimilars were more concentrated in the 50-64 and 65-74 age group.”

Add the high deductible category
Response: We thank the reviewer. We added information on high deductible in Table 1.

Table 2 also should contain more information. For example, the number (“28.6% were biosimilar prescriptions”) is not in Table 2. One way to solve this is to add a row for the combined total for IP and FP.
Response: The reviewers remark and proposal for the solution is greatly appreciated. We supplemented the proposed row in Table 2.

Discussion
The first paragraph is too long. Please divide it into two or more.
Response: We thank the reviewer for the valuable comment increasing the structure and readability of the manuscript. We shortened the introductory paragraph of the discussion and structured it by dividing it into several paragraphs.

(223-226) The authors compared the share of biosimilars in terms of total prescription (or claims) with that in market sales. This is similar to comparing apples to oranges because the prices of biosimilars are lower than those of reference drugs.
Response: The reviewer's comment is greatly appreciated. We, therefore, adapted the measure of comparison.

262: "Despite this growth, the biosimilars’ market share in Switzerland remained relatively low. In 2021, claims for reference products were four times higher than claims for biosimilars among all available biological products with biosimilars."

(234) The authors keep using the term "market share". It appears the authors used the term liberally. To use the term in a traditional sense, the study should have information on the revenue and prices of medication. To avoid confusion, please define the term early on.
Response: The reviewer's note is greatly appreciated. The term "Market share" was replaced by a more specific measure throughout the discussion section.

In Table A8, by coeff do the authors mean OR? Then use OR instead.
Response: We thank the reviewer for the comment. We have replaced it with "OR", instead.

Reviewer: 2
Dr. Jason Shafrin, FTI Consulting
Comments to the Author:
Abstract
• “Helsana, a leading Swiss health insurance”. In what sense is Helsana leading? Is it the most popular private health insurance? I would use a more concrete adjective or remove the term “leading” entirely.
Response: We appreciate the reviewer's comment. We specified the term “leading” in the abstract:

20: "The analysis is based on de-identified claims data of patients with mandatory health insurance at Helsana, one of the Swiss health insurances with a substantial enrollee base in mandatory health insurance."

• The abstract does not clarify which patients are included in the analysis. Not all diseases have a biosimilar. Is this only for disease that have an available biosimilar? Please clarify.
Response: We thank the reviewer for the important note. We specified the patients included in the study.

16: "The study included all patients who had at least one biosimilar available on the market at the time when they were prescribed a biologic product."

• “Increased relative price difference”. This term is not defined. Is this price difference between biologic and biosimilar? Is this measured as absolute difference or % of cost?
Response: The reviewer's comment is greatly appreciated as it addresses an important definition that
is crucial for the understanding of the study. We specified the relative price difference in the abstract.

30: “Increased relative price difference (difference in the price of available biosimilars relative to price of corresponding reference product)”

- It would be interesting to cite changes in overall biosimilar prescriptions vs. index prescriptions; patients may not want to change medications to a biosimilar if theirs is working, but may be more amenable for new prescriptions.

Response: We really appreciate this comment, as this is an important implication of our study. Therefore, we added one sentence in the abstract.

36: “The findings indicate that patients typically adhere to the therapy options initially chosen and are less inclined to make changes following the initiation of treatment.”

Background
- In general, the background is good. However, the background should also consider citing other studies that have examined how much biosimilars can reduce prices in different countries. For instance see: Maksabedian Hernandez et al. 2012

Response: The reviewer’s suggestion is greatly appreciated and is useful setting up the framework for the study. We have added the study in the “Background” section.

68: “A study conducted in the United States found that biologics can undergo price reductions ranging from -2.4% to -59.3% in response to biosimilar competition, with the extent of these reductions correlating with the adoption rate of biosimilars.”

Methods – Study design and population
- Why is the sample including all people with biologics and biosimilars? It could be the case that many of the biologics have no biosimilars. Thus, if biosimilar uptake was 100%, the study would still find less than 100% uptake since many biologics don’t have biosimilars available. Later (in the measures section) it says there is a more limited sample for people with biologics available.

Response: We thank the reviewer for pointing out a crucial concept of the methods. We included all individuals who, at the time of their initial prescription, had at least one biosimilar option available on the market. Consequently, we were able to investigate the factors associated with not prescribing biosimilars even when they were available. (It would not have made sense to include those initial prescriptions without available biosimilars option to assess factors for not prescribing, as they were not available on the market.) It’s worth noting that the reviewer’s observation is valid; in reality, the market share (proportion of claims) for biosimilars is lower due to the existence of biological products without any corresponding biosimilars available on the market.

To mitigate potential misunderstandings, we have incorporated the following additional sentences:

115: “The study included all patients who had at least one biosimilar available on the market at the time of IP of a biologic product. This enabled us to explore the determinants of non-prescription of biosimilars despite their availability.”

389: “It is worth noting that the actual biosimilars quota (proportion of biosimilars claims relative to
overall biological product claims), is lower in reality as there are biological products for which no corresponding biosimilars are available on the market. Nevertheless, even when considering this relatively higher observed quota, it remains comparatively low compared to other EU countries."

- Usually, you don’t report the N’s until the results sections.
Response: We thank the reviewer for the valuable comment. We moved the section of the exact derivation of the study population – as proposed – in the result section

188: “This research was conducted using a study population comprising 68’310 individuals who received at least one prescription for a biological or biosimilar medication between 2016 and 2021. For our study, we eliminated individuals who did not maintain continuous mandatory health insurance coverage throughout the entire observation period. This exclusion was implemented to mitigate potential bias in our regression analysis, resulting in a remaining sample size of 53’379 patients. Within this subgroup, there were 18’953 instances of initial prescriptions for biological medications that had a biosimilar alternative available at the time of dispensing.”

- Were patients required to be continuously enrolled for a specific time period to be included in the analysis?
Response: Yes, continuous enrollment during the observation period of patients curb the potential bias in our regression without harming the statistical power to much (68’310 to 53’379). We added one sentence in this regard:

191: “This exclusion was implemented to mitigate potential bias in our regression analysis, resulting in a remaining sample size of 53’379 patients.”

Methods - Measures
- Is the copay observed only if the patient fills the medication? If that is the case, this variable could be biased if people decide not to fill a prescription because the copay is too high. How do the authors take into account this potential bias.
Response: We appreciate the reviewer’s question. Indeed, if patients do not forward the invoice, then we do not see the claims of medications even if patients have received it. We were not able to delete this bias, we, therefore, have added a short paragraph explaining this bias in the limitation section.

379: “Furthermore, it is possible that invoices from individuals whose annual healthcare expenses did not surpass the annual deductible were not included in the analysis. Nevertheless, internal analyses conducted by Helsana indicated that this proportion accounts for approximately 1.5% of invoices, suggesting that any potential selection bias is likely minimal.”

- "comprehensive set of variables characterized the prescribed medications”. I wouldn’t say “comprehensive” since there is always missing information in every data set.
Response: We thank the reviewer for the note. We replaced the “comprehensive” with “broad” when writing about the dataset used throughout the manuscript.

Methods – Statistical Analysis
- "Chi-squared tests 150 were used to determine whether the prevalence was equivalent across the year”. Is this prevalence of biosimilar use among all patients using a biological product or only those where a biosimilar was available? Please be clear.
Response: We thank the reviewer for the valuable comment. We specified the population in this sentence.

168: “Chi-squared tests were used to determine whether the prevalence of biosimilars among all
patients using a biological product was equivalent across the years.

• "Three different logistic models with different sets of variables were computed (Table A8)." Explain why there were 3 different models.
Response: We thank the reviewer for the important remark. We addressed the reason for calculating 3 different model:

173: "We employed three distinct logistic regression models, each incorporating an additional set of variables, to comprehensively assess the impact of various factors on our study outcomes (Table A8). This approach allows us to explore multiple dimensions of influence and gain a more nuanced understanding of the relationships at play, enhancing the robustness and depth of our analysis."

• "Both, Model B and C, show similar results and a better fit of the estimates compared to Model A based on the goodness-of-fit criteria (AIC, BIC)." Explain what models A, B and C correspond to. Also, do not give results in the methods section.
Response: We added a description of the included variables in each model in following brackets.

177: "Both, Model B (sociodemographic + medication variables) and C (sociodemographic + medication + provider variables), show similar results and a better fit of the estimates compared to Model A (sociodemographic variables) based on the goodness-of-fit criteria (AIC, BIC)."

• It would be interesting to look at the time since biosimilar launch as well as uptake make take some time.
Response: We thank the reviewer for this suggestion. We believe this variable is important when looking at biosimilars uptake. However, we have calculated it and for this study it was not appropriate. The reason is the combination of an uneven distribution of prescriptions on the time since marketing approval and corresponding the number of prescriptions (statistical power).

Results
• The results section seems to be limited to people with prescriptions where there is a biosimilar substitute. This makes sense but throughout the methods this is not clear.
Response: The reviewer's feedback is greatly appreciated as it addresses the readability of the paper. Addressing various feedback regarding this point during the review process, we clarified this throughout the manuscript the analysis and we also added one introductory sentence under "statistical analysis":

160: "All statistical analysis were performed at the study population that consisted of individuals who had at least one biosimilar available on the market at the time of IP of a biologic product."

• A CONSORT table / CONSORT diagram is needed.
Response: We the reviewers request for a CONSORT table in our manuscript, but as our study is observational and based on claims data, we do not believe it falls within the scope of CONSORT guidelines, which are designed for clinical trials. Moreover, our previously published study with a similar methodology (Opioid prescriptions after knee replacement: a retrospective study of pathways and prognostic factors in the Swiss healthcare setting, DOI: 10.1136/bmjopen-2022-067542) did not include a CONSORT table. To ensure consistency and adherence to best practices for reporting observational studies, we have followed the STROBE guidelines to enhance transparency in our manuscript.

• For Table 1, it seems that this analysis is at the patient-index prescription (IP) level rather than the patient level, because you state that there were "17'654 individuals (or 18'953 IPs, respectively)". Thus, be clear that the table is at the patient-IP level not the patient level. You may want to consider a
patient characteristics table where you look at patient characteristics based on first IP so you are not double counting individuals. That would be a useful sensitivity analysis.

Response: We thank the reviewer for pointing out the need for clarification and order. We agree that the reader might be confused reading this part of the paper. Therefore, we adapted it by rephrasing the introductory paragraph and cancelling the paragraph on the individual patient level.

• How representative is the study population compared to the general Swiss population? 

Response: We appreciate the reviewer's question. We provided further information regarding the representativeness of the Helsana database.

Hence, earlier research has suggested that this database can be considered reasonably representative of the broader Swiss population, given that the findings revealed only minimal disparities between unadjusted and adjusted results.

• "15.1% (2'672 patients) received multiple biosimilars". Is this multiple biosimilar prescriptions are two different types of drug? Please clarify.

Response: In response to a prior reviewer's feedback, we have removed this paragraph from the manuscript. Consequently, there are no additional steps or actions needed in this regard.

• Wouldn't the results be impacted by the composition of the drugs. For instance, it could be that biosimilar % rises over time for every reference product. However, as new biosimilars enter, they are then added to your data set at low initial uptake rates. Thus, you may want to re-run the analysis looking at years since biosimilar launch to see if that increases monotonically over time. We do see some increase in biosimilar use in the regression and certainly it is the case that more biosimilars available increase biosimilar usage.

Response: We thank the reviewer for this input. This reviewer's comment has been addressed previously.

• The large switch between biosimilars to reference products is surprising. It would be useful to discuss why you think this is happening in the discussion.

Response: We sincerely value this comment, and we acknowledge the significance of this intriguing result. Considering the limited existing literature on the factors driving switches from biosimilars to reference products, our approach primarily emphasizes the need for additional research in this area. We refrain from delving extensively into the specifics of why patients make such switches, thus prompting further investigation into this complex and crucial aspect of healthcare decision-making.

The substantial transition from biosimilars to reference products observed in our study warrants discussion. While our analysis didn't delve into the specific drivers behind this shift, several factors may contribute to it. These could encompass the beforementioned patient and physician preferences. Further exploration of these factors is essential to gain a comprehensive understanding of the dynamics between biosimilars and reference products in clinical practice, shedding light on the implications for healthcare stakeholders and policymakers.

• "In terms of pharmaceutical variables, monoclonal antibodies, LMW heparins and growth factors were associated with substantially lower biosimilar IP occurrences (-88.5%, -99.9% and -84.2%) than fusion proteins." Are these percentages or absolute differences. I assume the former but please clarify.

Response: We thank the reviewer the proposition to double check the numbers. Indeed, it is the former (because of the statistical power of each medication category).

Discussion
• You may want to link the statement “Moreover, the current incentive system discourages the prescription of biosimilars for self-dispensing doctors and pharmacies as they are rewarded for prescribing the more expensive product by a bigger profit margin” to your finding that physicians switch from biosimilar to reference in the data.
Response: This valuable suggestion is greatly appreciated. This insightful input prompted us to incorporate the idea, and we have adapted our manuscript accordingly.

296: “Moreover, the finding that patients frequently switch from biosimilar to reference products underscores the complex landscape surrounding biosimilar utilization. This phenomenon may, in part, be influenced by the current incentive system discourages the prescription of biosimilars”

• For biosimilars, one would guess that that these would work nearly identically to the reference product. However, reimbursement is lower and it could be the case that manufacturing quality is less consistent. If there is evidence of that, it may be useful to cite that; if not feel free to ignore this comment.
Response: Indeed, that would represent a logical rationale supporting our finding. Nevertheless, we were unable to find any pertinent information that could be referenced.

• “The strongest barrier for biosimilar prescriptions was the increasing relative price difference between biosimilar and reference product”. Why is this a barrier? The authors state that this is because physicians are unfamiliar with them, but why does price impact this? Is this because physicians consider price to play a signaling role for quality?
Response: We appreciate the reviewer's comment. We reformulated, as these “barriers” are really just a synonym for the “highest association of not prescribing biosimilars”.

327: “Our findings showed that biosimilars with high relative price difference to reference product were less likely prescribed. Several factors contribute to physicians’ reduced prescription rates in association with the lower prices of biosimilars.”

• The stockpiling of different medications is a very interesting point. A reason against diversifying to biosimilars if you’d need to store the brand also.
Response: we thank the reviewer for highlighting this interesting aspect of stockpiling medications. While it's indeed an intriguing point, we believe that, in the context of our study, it does not require specific action within the manuscript. However, we recognize its relevance and will keep it in mind for future research and discussions on this topic.

*** ***

COI statements:

Reviewer: 1
Competing interests of Reviewer: None.

Reviewer: 2
Competing interests of Reviewer: I am an employee of FTI Consulting, a consulting firm to life science, medical care, government and non-profit health care sectors among others.
| REVIEWER       | Shafrin, Jason  
|               | FTI Consulting |
| REVIEW RETURNED | 24-Oct-2023   |
| GENERAL COMMENTS | These revisions address my previous comments. I have no further comments. |