Dear Editor,

We want to thank you and the peer reviewers for the rapid review of our submitted manuscript titled as “Real-world clinical outcomes, direct medical costs, and cost-effectiveness associated with infliximab maintenance therapy for moderate to severe Crohn’s disease in China” (Manuscript NO.: 57683). We have carefully reviewed the comments from the peer reviewer and the scientific editor and revised our manuscript according to these raised comments. All revisions and updates have been highlighted in the word version with tracking changes. Our responses to the raised comments are listed below using point-to-point style.

Responses to the comments from Peer Reviewer

1. L 73-76: Please specify the comparator of ACCENT 1. You write "In this trail [sic], there was a significantly higher clinical remission rate, a higher mucosal healing rate, and a lower hospitalization rate associated with one-year infliximab MT (IMT)", leaving the reader wondering compared to what?

   Response: We agree with this comment and have revised this sentence by adding the comparator (placebo) used in ACCENT 1 trial. The revision to address this comment can be found from Line 77 to 78 in the revised manuscript.

2. L 82-87: The manuscript would benefit from discussing other relevant comparators to infliximab (biologics). E.g. other TNF-alpha inhibitors (e.g. etanercept, adalimumab, vedolizumab) and IL-12 and 23 inhibitor ustekinumab. If they are not available to Chinese patients this should be clarified. If they are available, the paper should include a discussion on why they were not considered as comparators. If previous cost-effectiveness analyses have been done on these comparators in the relevant setting, they should be discussed. Especially if any comparisons have been done with infliximab.

   Response: we truly appreciate this thoughtful comment from the reviewer. Except infliximab, the other launched TNF-alpha inhibitors before our study included etanercept and adalimumab. However, the approved indications for etanercept and adalimumab in China didn’t include CD. Vedolizumab was approved for CD in China in this March. Ustekinumab was approved for CD in this March as well. Thus, infliximab was the only biologic approved for CD in China when we started this study in 2018. With more and more approved biologics for CD in China, we definitely see the needs of evidence to clarify their cost-effectiveness for moderate to severe CD in China. Thus, we have added some contents in the discussion regarding the newly approved biologics for CD and their impact on the treatment landscape in Chinese patients with moderate to severe CD. The revision to address this comment can be found from Line 357 to 366 in the revised manuscript.

3. L 171-181: The study groups seem to significantly differ in important characteristics (such as age and comorbidities). What are the implications of this? Did you take into account how the differences in outcomes may be attributed to differences between study groups? For example, if younger patients in general have a higher level of QoL some of the QoL benefit in the IMT group should be attributed to the younger average age in the IMT group. This should be explained more thoroughly.

   Response: We fully agree with this comment that the differences in patient characteristics could confound the measured outcomes and bias the comparisons between the two study groups. That is why our study conducted multivariate regression analyses to adjust the potential confounding effects associated with patient characteristics (please see Line 118 to 123). The results of these regression analyses were reported from Line 187 to 198. To further help the readers to understand the methods we used to adjust the confounding effects associated with patient characteristics, we have revised the manuscript by specifying the patient characteristics in the multivariate regression analyses. Further, we have added the three tables (Tables 3, 4, and 5) for the results of these multivariate regression analysis to demonstrate the specific characteristics we have adjusted for the comparisons of the outcomes associated with the two study groups (IMT vs. CMT) in the revised manuscript. The revision to address this comment can be found from Line 128 to 136, Line 225 to 228, and added tables (3, 4, and 5).

4. One study group only comprise 130 patients. Please include a discussion on potential problems and inherent uncertainties related to such small patient samples. Did you have outliers?

   Response: We agree with this comment that the number of the included patients was not large enough to represent the moderate to severe CD patients across China. However, our study setting was a regional treatment center for inflammatory bowel disease in the east China. As the incidence of CD in China is relatively low (0.46/1,000,000), it is challengeable to create a large study group of moderate-to-severe CD in a single treatment center. Thus, we have revised the manuscript to acknowledge this limitation and compare our patients to the moderate-to-severe patients in other Chinese observational studies to support the generalizability of our study cohort. The revision to address this comment can be found from Line 375 to 383.

5. Describe more in-depth the treatment patterns of infliximab. Do you have information on how closely patients followed recommended infliximab use (in terms of induction and maintenance doses)? What is the recommended use? Describe how you defined induction and maintenance periods in the model.

   Response: we accepted this comment. We have added the recommended information in the revised manuscript by making definition of induction therapy and maintenance therapy, reporting the distributions of induction therapy and maintenance therapy, and

reporting the administration information of infliximab used as induction therapy and maintenance therapy in our study patients. The revision to address this comment can be found from Line 151 to 163.

6. As the utilities seem to have a very large impact on the results, you should use sensitivity analyses with other utilities from a different source, e.g. based on infliximab trial or from other literature. Especially since the model uses utilities estimated from so few patients, with some uncertainties regarding the study method.

   Response: we agree with this comment that the quality of life (utility) has a large impact on the cost-effectiveness of IMT due to a large confidence interval of the estimated utility from small study sample size. Because the utility was used to directly calculate quality-adjusted life years in the cost-effectiveness model and any slight change of the utility is going to substantially change the cost-effectiveness of IMT. We have found a systematic review reporting the pooled estimations for the utility associated disease remission and active disease from 17 studies. Our estimations are highly comparable to the estimations in this meta-analysis (disease remission: 0.829 vs. 0.840; active disease: 0.743 vs. 0.753). Thus, the validity of the utility variables in our cost-effectiveness analysis should be reasonable. The revision to address this comment can be found from Line 337 to 347.

7. L224-227: Please comment on the sensitivity results in relation to base-case.

   Response: the purpose of sensitivity analysis was to assess the impact of uncertainty associated with model variables on the cost-effectiveness of IMT. Thus, we can use the sensitivity analysis to estimate the distribution of cost-effectiveness result, which could be used to assess the robustness of base-case analysis result. We revised the manuscript by explaining the rationale of sensitivity analysis and how to use the sensitivity analysis to support the robustness of base case analysis. The revision to address this comment can be found from Line 347 to 355.

8. L259-260: This doesn't seem to make sense. Shouldn't it instead say that the infliximab acquisition cost is likely the main cost driver? (Rather than cost-effectiveness driver).

   Response: the cost-effectiveness analysis used incremental cost-effectiveness ratio (ICER) as the result to measure cost-effectiveness. ICER was calculated through dividing the difference in lifetime medical costs by the difference in quality-adjusted life years associated with the two model scenarios (IMT vs. CMT). Thus, the acquisition costs of infliximab drove the lifetime medical costs and also the ICER, the indicator for cost-effectiveness of IMT. The revision to address this comment can be found from Line 310 to 311.

9. Some spelling errors: e.g. "trail" instead of "trial", double spaces in some places, very long sentences which would benefit from being split into shorter sentences.

Response: we want to thank the reviewer to point out this typo in the manuscript. We have gone through the whole manuscript to correct this typo. Additionally, we have further improved the language throughout the manuscript.

Responses to the comments from Science Editor

1. I found the title was more than 20 words. The title should be no more than 20 words;

   Response: We have changed the title to "Real-world cost-effectiveness of infliximab maintenance therapy for moderate to severe Crohn's disease in China"

2. I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

   Response: we will upload the scanned copy of the grant approvals alone with the submission of the revised manuscript. The grant number will be highlighted in yellow colour in the uploaded grant approval documentations.

3. I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

   Response: we have followed the instructions to create the manuscript figures using PowerPoint for the resubmission.

4. I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

   Response: we have followed the instructions to add PMID and DOI associated with the references cited in the revised manuscript.

5. I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text.

   Response: we have followed the instruction to add article highlight section in the end of the manuscript.

Additionally, we have also revised the manuscript according to STROBE check list. Once again, we want to thank you and the peer reviewers for the review and the valuable comments.

Should you have any further comments on our revised manuscript, we would be very happy to address them until it meets the publication standard in the World Journal of Gastroenterology.

Sincerely yours,

Qian Cao