To the editor:

Thank you for sharing the remarks of the reviewers. I would like to make the following responses to the issues raised from the review of my submission:

Reviewer 1:
This type of bibliometric studies about important topics are very welcomed, because describe very clearly the interest of the research about different areas of the world, together with the type of interest, the number of studies performed in every country and the citation times and impact of different Journals used Taken all together we obtain a clear message and the importance of the different aspects of an important diseases around the world. In the present manuscript the authors gives a clear overview of the iron deficiency anemia and their bibliographic trends over the past 20 years.

I thank Reviewer 1 for his/her comments. There were no specific edits requested by this reviewer.

Reviewer 2:
1. "All articles were searched using the Clarivate Analytics World of Science Core Collection (WOSCC) on August 30, 2020." The method is not appropriate. the title of the manuscript is "Trends in iron deficiency anemia research 2001-2020: a bibliometric analysis". It is impossible to know the number of articles in 2020 in World of Science Core Collection on August 30, 2020. The database used is not appropriate. Web of Science Core Collection includes Web of Science Core Collection: Citation Indexes 1. Science Citation Index Expanded (SCI-EXPANDED) -- 1900-present 2. Social Sciences Citation Index (SSCI) -- 1900-present 3. Arts & Humanities Citation Index (A&HCI) -- 1975-present 4. Conference Proceedings Citation Index - Science (CPCI-S) -- 1990-present 5. Conference Proceedings Citation Index - Social Sciences & Humanities (CPCI-SSH) -- 1990-present 6. Book Citation Index– Science (BKCI-S) -- 2005-present 7. Book Citation Index– Social Sciences & Humanities (BKCI-SSH) -- 2005-present 8. Emerging Sources Citation Index (ESCI) -- 2015-present Web of Science Core Collection: Chemical Indexes 1. Current Chemical Reactions (CCR-EXPANDED) 2. Index Chemicus (IC) Web of Science Core Collection is designed mainly for researchers to find published literature, not for bibliometric studies. It is unsuitable to use all of these different levels of databases. For example, ESCI complements the highly selective indexes by providing earlier visibility for sources under evaluation as part of the rigorous journal selection process of SCI-EXPANDED, SSCI, and A&HCI.

I agree that every database has limitations. Regarding the appropriateness of the Web of Science Core Collection for bibliometric studies, the Clarivate Web of Science website states that the Web of Science Core Collection "is the standard data set for 'bibliometric' analysis for identifying and monitoring research trends" (https://clarivate.libguides.com/webofscienceplatform/coverage). The Web of Science Core Collection has been used in bibliometric analyses in the literature, for example Kawiki J and Yu X: Bibliometric Analysis of Ebola Research Indexed in Web of Science and Scopus (2010-2020); https://doi.org/10.1155/2020/5476567. There are numerous examples of bibliometric studies in literature that use the Web of Science without indicating whether it is the Core Collection – based on the endorsement of Clarivate, it is likely that a great many of these were conducted using the Web of Science Core Collection.

2. "The study used publicly available data, and thus ethical approval was not required. The search criteria were topic ("iron deficiency anemia"), limited to document type (article OR review), language (English), and time span (2001-2020)." The authors noticed "All articles were searched using the Clarivate Analytics World of Science Core Collection (WOSCC) on August 30, 2020." Why is "document type (article OR review)"? The results cannot be repeated that is a basis of scientific research.

The search was limited to articles and reviews because I was primarily interested in these types of publications rather than editorials, letters to the editor, etc. that would minimally impact the advancement of the science of iron deficiency anemia. This is a common technique in the systematic reviews and the bibliometric literature, the purpose of which is to focus on the most important publications on a given topic (e.g. Huang, L., Shi, X., Zhang, N. *et al.* Bibliometric analysis of trends and issues in traditional medicine for stroke research: 2004–2018. *BMC Complement Med Ther* **20,** 39 (2020). https://doi.org/10.1186/s12906-020-2832-x; Lu C et al. Top-100 Most Cited Publications Concerning Network Pharmacology: A Bibliometric Analysis. Evidence-based Complementary and Alternative Medicine 2019:1-7). In the case of iron deficiency anemia, where it was anticipated that there would be a large volume of studies, this is an important step to ensure a high quality of the articles resulting from the search.

3. The search keywords is not appropriate so that the authors missed some related papers, …
I agree that the search strategy is a key component of a bibliometric study. However, I would like to point out that the search was a topic search and was <u>not</u> limited to a search of the titles and keywords, as stated in the Methods section of the manuscript (p5 lines 7-9). A "topic search" in Web of Science will search the following parameters: "1) The **Title** of the article, review, proceeding, book, etc. 2) The **Abstract**, which is the work's summary containing the key points discussed such as research question, methodology, discussion and conclusion. This field is supplied by the author(s) of the article or paper.3) The **Keywords** and **Keywords Plus** fields: The *keywords* field is the one supplied by the author(s) and "tags" the main and subtopics of the paper's content. The *keywords plus* field is an algorithm that provides expanded terms stemming from the record's cited references or bibliography. Note that a "topic search" can be performed when doing a bibliometric analysis (for an example, Jian-Hua Xie, Ming-Liang Jin, Gordon A. Morris, Xue-Qiang Zha, Han-Qing Chen, Yang Yi, Jing-En Li, Zhi-Jun Wang, Jie Gao, Shao-Ping Nie, Peng Shang & Ming-Yong Xie (2016) Advances on Bioactive Polysaccharides from Medicinal Plants, Critical Reviews in Food Science and Nutrition, 56:sup1, S60-S84, DOI: 10.1080/10408398.2015.1069255). I clarified the search methodology, in particular the definition of a topic search in the revised manuscript (p6 lines 9-11).

The reviewer provided a list of 103 articles: I evaluated them for 1) whether they were included in the search results, 2) their citation rate, and 3) whether they were appropriate to the topic of iron deficiency in humans. <u>91 of these papers were included in my original search</u> and were analyzed in the original version of the manuscript. Of the remaining 12 articles, 1 was indexed after the original search date and 1 was a case report and was therefore not included in the search. 5 were not indexed in Web of Science and were also not included. The remaining 5 articles, although listed in Web of Science, were not indexed under the topic of iron deficiency anemia based on title, abstract, keyword, and keywords plus. I retrieved the full text of these 5 papers and reviewed their contents, and I agree with the categorization of the papers in Web of Science. Moreover, their citation rate of these papers was below that of the top 10-cited papers from each category in the subset analysis. I summarize the findings from my review of these 12 papers not included in the search in the below table:

Reference	Comment	Topics (if listed in WoS, meeting search criteria, and indexed before search date)	Citations (if listed in WoS, meeting search criteria, and indexed before search date)
Shand, A.W., Bell, J., Henry, A., Grzeskowiak, L.E., Kidson-Gerber, G., Pearson, S. and Nassar, N. (2020), Rapid increase in intravenous iron therapy for women of reproductive age in Australia. Medical Journal of Australia, 213 (2), 85-86.	Indexed after search date	N/A	N/A
Song, J.X., Wen, Y., Li, R.W., Dong, T., Tang, Y.F., Zhang, J.J. and Sa, Y.L. (2020), Phenotypic characterization of macrophages in the BMB sample of human acute leukemia. Annals of Hematology, 99 (3), 539-547.	Not categorized under iron deficiency anemia	Author Keywords:Macrophage; Phenotype; Acute leukemia; Bone marrow of biopsy; Immunohistochemistry; KeyWords Plus:CD163 EXPRESSION; CELL; CANCER; TARGET	0
Qassim, A., Grivell, R.M., Henry, A., Kidson-Gerber, G., Shand, A. and Grzeskowiak, L.E. (2019), Intravenous or oral iron for treating iron deficiency anaemia during pregnancy: systematic review and meta-analysis. Medical Journal of Australia, 211 (8), 367-373.	Not listed in Web of Science	N/A	N/A
Aggarwal, S.N., Cavanagh, Y., Wang, L., Akmal, A. and Grossman, M.A. (2019), Upper Gastrointestinal Crohn's Disease: Literature Review and Case Presentation. Case Reports in Gastrointestinal Medicine, 2019, Article Number: 2708909.	Case report	N/A	N/A
Chen, L.W., Wahlqvist, M.L., Teng, N.C. and Lu, H.M. (2009), Imputed food insecurity as a predictor of disease and mental health in Taiwanese elementary school children. Asia Pacific Journal of Clinical Nutrition, 18 (4), 605-619.	Not categorized under iron deficiency anemia	Author Keywords:food insecurity; disease; mental health; health expenditure; children KeyWords Plus:LOW-BIRTH-WEIGHT; OVERWEIGHT; NUTRITION; INJURIES; SECURITY; RISK; DIET; LIFE	10
Shreeve, W.W. (2007), Use of isotopes in the diagnosis of hematopoietic disorders. Experimental Hematology, 35 (4), 173-179.	Not categorized under iron deficiency anemia	Author Keywords: (none) KeyWords Plus:EXTRAMEDULLARY HEMATOPOIESIS; MARROW; ANEMIA	6
Vendt, N., Grunberg, H., Leedo, S., Tillmann, V. and Talvik, T. (2007), Prevalence and causes of iron deficiency anemias in infants aged 9 to 12 months in Estonia. Medicina-Lithuania, 43 (12), 947-952.	Not listed in Web of Science	N/A	N/A
Yeh, J.S. and Cheng, C.H. (2005), Using hierarchical soft computing method to discriminate microcyte anemia. Expert Systems with Applications, 29 (3), 515-524.	Not categorized under iron deficiency anemia	Author Keywords: ANFIS reasoning in medicine; microcyte anemia; hierarchical soft computing KeyWords Plus:IRON-DEFICIENCY; SYSTEM	7
Vacca, A., Ria, R., Ribatti, D., Semeraro, F., Djonov, V., Di Raimondo, F. and Dammacco, F. (2003), A paracrine loop in the vascular endothelial growth factor pathway triggers tumor angiogenesis and growth in multiple myeloma. Haematologica, 88 (2), 176-185.	Not categorized under iron deficiency anemia	Author Keywords:angiogenesis; endothelial cells; multiple myeloma; stromal cells; tumor growth; vascular endothelial growth factor KeyWords Plus:BONE-MARROW ANGIOGENESIS; TYROSINE KINASE; CELL-GROWTH; UNDETERMINED SIGNIFICANCE; MONOCLONAL GAMMOPATHY; SIGNAL-TRANSDUCTION; EXPRESSION; RECEPTOR; VEGF; LYMPHANGIOGENESIS	113
Bradley, R.H. and Corwyn, R.F. (2005), Caring for children around the world: A view from HOME. International Journal of Behavioral Development, 29 (6), 468-478.	Not listed in Web of Science	N/A	N/A
Mercer, J.S. (2001), Current best evidence: A review of the literature on umbilical cord clamping. Journal of Midwifery & Womens Health, 46 (6), 402-414.	Not listed in Web of Science	N/A	N/A
Henderson, H.A. and Wachs, T.D. (2007), Temperament theory and the study of cognition-emotion interactions across development. Developmental Review, 27 (3), 396-427.	Not listed in Web of Science	N/A	N/A
Steckel, R.H., Rose, J.C., Larsen, C.S. and Walker, P.L. (2002), Skeletal health in the Western Hemisphere from 4000 BC to the present. Evolutionary Anthropology, 11 (4), 142-155.	Not listed in Web of Science	N/A	N/A

I think this exercise provides further validation of the search methodology described in this manuscript. The results of my search of Web of Science on which the manuscript is based can be obtained from me upon reasonable request.

4. "The following data were extracted from these articles: year of publication, journal, study design, country of first author, and number of citations." The authors noticed that "The study used publicly available data, and thus ethical approval was not required. The search criteria were topic ("iron deficiency anemia"), limited to document type (article OR review), language (English), and time span (2001-2020)." Why is "from these articles"?

I apologize that I do not understand the reviewer's question. The data analysis was performed on the articles identified in the search. Therefore, "these articles" were the articles identified from the search. Without further clarification it would be difficult for me to further address the question.

5. "The entire list of retrieved articles was analyzed, and an additional subset analysis of the articles grouped by publication in 5-year increments (2001-2005; 2006-2010; 2011-2015; 2016-2020) was performed. The top 25 keywords identified in the title and abstract of each publication in each time interval was compiled." Reference is needed. The original paper is recommended for more details.

The reference has been added to the revised version of the manuscript (p7 line 1).

6. "The search returned 4828 references. Review of the titles, abstracts, and full texts of the top 200 cited papers in this group was performed to assess the quality of the search, and all papers in this group were appropriate to the topic of iron deficiency anemia." The results cannot be repeated that is a basis of scientific research.
I think the reviewer is referring to his concerns about the search strategy, which I addressed in points 2 and 3. Regarding the review of the top 200 papers to validate the search, it is an accepted practice to review a subset of the references to assess for appropriateness to topic. See references 7 and 8.

7. A total of 5,561 English documents including 4,782 English articles and 779 English reviews were search out from Web of Science Core Collection from 2002 to 2020. (Data last updated: 31 March 2021) It should be noticed that is impossible to know the number of publications in 2020 on 31 March 2021.
I apologize that I do not see the cited text in my manuscript. Without further clarification I cannot comment.

8. "These publications had an h-index of 137 with an average of 25.42 citations per item. The number of papers published per year in this study has varied from 124 to 402." The results cannot be repeated that is a basis of scientific research.
I think this point refers to the reviewer's concerns about the search strategy, which I addressed above. In addition, I am referring to the set of papers identified by the search strategy performed using the database (see points 2, 3, and 7).

9. "The year with the largest number of papers published in this study was 2019." This is not correct. The method is not accepted in this study.
I think this point refers to the reviewer's concerns about the search strategy, which I addressed in points 2 and 3.

10. "The rate of publication of papers in this study has varied from 2.568% to 8.326% (Figure 1)." The study design is not accepted. Results in Fig. 1 is not correct.
I think this point refers to the reviewer's concerns about the search strategy, which I addressed in points 2 and 3.

11. "Based on WOSCC metadata, the papers were published in 97 different research areas, of which the most common were nutrition and dietetics (n=672, 13.919% of total), gastroenterology (n=610, 12.635%), hematology (n=570, 11.806%), pediatrics (n=566, 11.723%), and general internal medicine (n=522, 10.812%)." The study design and method are not accepted. Thus, all related results are not appropriate.
I think this point refers to the reviewer's concerns about the search strategy, which I addressed above (points 2 and 3).

12. "In total, publications were contributed by 157 countries, with the top ten publishing countries listed in Figure 2." England is not a country. The study design and method are not accepted. Thus, all related results are not appropriate.

"England" is defined by the Harper-Collins dictionary as "the largest constituent <u>country</u> of the United Kingdom, bordering on Scotland and Wales …" . Another reference is Hirsch ED et al. <u>The new first dictionary of cultural literacy,</u> New York, Haughton-Mifflin, p197: "**England is a country** in northwest EUROPE . Along with SCOTLAND, NORTHERN IRELAND , and Wales , it is part of the UNITED KINGDOM ."

Regarding the search strategy, which I think was also part of this question, see points 2 and 3.

13. "The United States has contributed the largest number of the papers. Other nations in the top 5 countries of publication were Turkey, China, Italy, and England." England is not a country. The study design and method are not accepted. Thus, all related results are not appropriate.

Again, I think this statement refers to the search strategy, which I address in points 2 and 3. England is a country (see point 12).

14. "The authors in this study represented 4,840 institutions. The institutions contributing the most papers to this study were the University of California system (n=179 records) and Harvard University (n=126 records). 2,411 funding agencies were listed in these publications, of which the largest number of studies were funded by the United States Department of Health and Human Services (n=448), the National Institutes of Health (United States, n=431), and the National Natural Science Foundation of China (n=119)." The study design and method are not accepted. Thus, all related results are not appropriate.

Again, I think this statement refers to the search strategy, which I address in points 2 and 3.

15. "The collaboration network analysis is illustrated in Figure 3 and includes countries contributing at least 10 papers. Using this criterion, 64 countries are included in the analysis. There are 3 nodes identified using international collaboration data. The largest, illustrated in red, includes the United States, Canada, and India as the largest contributors. The second, illustrated in blue, includes Turkey, China, and Japan as the most prominent contributing members. The third, illustrated in green, includes England and many European countries." England and Scotland are not countries. The study design and method are not accepted. Thus, all related results are not appropriate.

I am uncertain what the reviewer means by this statement. If the reviewer is referring to the search methodology, I have addressed this point above (points 2 and 3). If the reviewer's question pertains to the data mapping process and its objectivity and reproducibility, these issues are addressed in a paper by van Eck and Waltman, which I have added as a reference to the revised version of the manuscript (p5 line 17). Regarding England, see point 12. Scotland is likewise a country. Both are regarded as such by Web of Science.

16. "The papers in this study were published by 1,365 journals. 659 journals published ≥1 paper." The authors noticed that "The papers in this study were published by 1,365 journals". How do the authors have "659 journals published ≥1 paper"? Do the authors mean 697 journal published < 1 paper? How do the journals published < 1 paper? What does "< 1 paper" mean?

What this statement means is that 659 journals published ≥1 paper; the remaining journals published 1 paper apiece. I have clarified this statement in the revised version of the manuscript (p10 lines 3-4).

17. "The top 15 journals, with the number of articles published and the journal's impact factor (IF), drawn from the 2017 Journal Citation Reports of Clarivate Analytics) are shown in Table 1." It is 2021 now. Why do the authors used the journal's impact factor (IF), drawn from the 2017 Journal Citation Reports of Clarivate Analytics?
I have updated the manuscript to include the latest available IFs (2020) (p11 line 6 and Table 1).

18. "The IF for the journals in this group ranged from 16.601 (Blood) to 1.076 (Journal of Pediatric Hematology Oncology and Pediatric Hematology and Oncology). The largest number of papers were published by Journal of Nutrition (n=107), PLOS One (n=81), and World Journal of Gastroenterology (n=76)." The study design and method are not accepted. Thus, all related results are not appropriate.
Again, I think this statement refers to the search strategy, which I address above (points 2 and 3).

19. "Overall, 123 terms appeared 50 times or more in the titles or abstracts of the papers in this study (Figure 4). For example, "iron deficiency anemia" appeared 1533 times, "anemia" appeared 1252 times, "children" appeared 726 times, "iron deficiency" appeared 627 times, and "prevalence" appeared 608 times." The authors noticed that "The search returned 4828 references." and "iron deficiency anemia" appeared 1533 times". Lots papers are not related to "iron deficiency anemia".
I think the reviewer is unclear about the search strategy: because this is a topic search, an article could be included if the term iron deficiency anemia did not appear in the title, abstract, or keywords but did occur in the keywords plus field.

20. "Based on the VOSviewer keyword mapping, the terms or phrases associated with iron deficiency anemia were divided into 5 clusters, represented by 5 colors (red, green, blue, yellow, and purple)." What kinds of keywords do the authors discuss?
These are the keywords chosen by the authors. This has been clarified in the revised version of the manuscript (p13 line 1).

21. "From the results of co-occurrences, current iron deficiency anemia research was shown to be mainly focused on 5 major areas. These are 1) epidemiologic aspects of iron deficiency anemia (red) 2) biochemical aspects of iron deficiency anemia (green), 3) clinical evaluation of causes of iron deficiency anemia (blue), 4) causes of iron deficiency anemia (yellow), and 5) bioavailability of dietary iron (purple). These 5 topics may thus be regarded as the current research hotspots in the field of iron deficiency anemia." What are their development trends? It should be in "Trends in iron deficiency anemia research 2001-2020: a bibliometric analysis"
This statement has been modified to read: "**These 5 topics may thus be regarded as the research hotspots in the field of iron deficiency anemia between 2001-2020** (p12 lines 12-13)."

22. "A subset analysis of the top 25 keywords of each 5-year interval between 2001-2020 and coded to the 5 areas presented in Figure 4 is presented in Table 2." This idea has been proposed. Reference is needed. The original paper is recommended for more details. Zhang, G.F., Xie, S.D. and Ho, Y.S. (2010), A bibliometric analysis of world volatile organic compounds research trends. Scientometrics, 83 (2), 477-492.
This reference has been added to the revised manuscript (p13 line 2).

23. "The top 10 cited papers published for the entire period 2001-2020, and the top 10 cited papers published in each 5-year interval are listed in Table 3." Many the top 10 cited papers published for the entire period 2001-2020, and the top 10 cited papers published in each 5-year interval in Table 3 are not related to "Trends in iron deficiency anemia research 2001-2020: a bibliometric analysis". They do

not contain search keywords "iron deficiency anemia" in their title, abstract, and author keywords, for example …

See the answer to point 19. There were papers identified by the search in which the term iron deficiency anemia occurred only in the keywords plus field. The topics, abstracts, keywords, and keywords plus were reviewed for these publications (see point 6). Moreover, several of these papers are cited in the discussion section of the manuscript and their relationship to the topic is emphasized.

24. In addition, there are two "Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia" in Table 3. They have different reference numbers 18 and 20. However, the number of 20 reference in the reference section is not the one in Table 3. "The total number of citations per paper for the top 10 cited papers published from 2001-2020 ranged from 752 to 4084." The results cannot be repeated that is a basis of scientific research. Thus, all related results are not accepted.

This error has been corrected. In addition, all references in the Table 3 have been renumbered since additional references were added at the request of Reviewer 2. In addition, I think this statement also refers to the issues I discussed above (see points 2, 3, 6, 9-15).

25. "Discussion" The study design, search keywords, and methods are not accepted. Thus, all discussions are not appropriate

I think this statement refers to the issues I discussed above (see points 2, 3, 6, 9-15).

26. "This bibliometric analysis was performed to evaluate the research trends in the field of iron deficiency anemia between 2001-2020." Study design is not accepted.

I think this statement refers to the issues I discussed above (see points 2, 3, 6, 9-15).

27. "The purpose of this study was 1) to identify and analyze scientific publications in this field" The study design, search keywords, and methods are not accepted. Thus, the authors missed miss some of related papers. Also, included lots of papers that do not contain search keywords in their title, abstract, and author keywords. In addition, the results cannot be repeated that is a basis of scientific research.

I think this statement refers to the issues I discussed above (see points 2, 3, 6, 9-15).

28. "to compare the contribution of this research in different countries and institutions." The study design, search keywords, and methods are not accepted. Thus, related discussions are not appropriate.

I think this statement refers to the issues I discussed above (see points 2, 3, 6, 9-15).

29. "The main findings were 1) that the most common topic areas were nutrition and dietetics, gastroenterology, hematology, pediatrics, and general internal medicine" The study design, search keywords, and methods are not accepted. Thus, related discussions are not appropriate.

I think this statement refers to the issues I discussed above (see points 2, 3, 6, 9-15).

30. "United States-based researchers contributed to the vast majority of papers, although researchers from Turkey, China, Italy, and England also made significant contributions to the literature" The study design, search keywords, and methods are not accepted. Thus, related discussions are not appropriate. England is not a country.

I think this statement refers to the issues I discussed above (see points 2, 3, 6, 9-15). England is a country – see point 12.

31. "keyword analysis revealed that 5 research areas have developed as current hotspots: epidemiologic aspects of iron deficiency anemia, biochemical aspects of iron deficiency anemia, clinical evaluation of causes of iron deficiency anemia, causes of iron deficiency anemia, and bioavailability of dietary iron" The study design, search keywords, and methods are not accepted. Thus, related discussions are not appropriate. What are their development trends? It should be in "Trends in iron deficiency anemia research 2001-2020: a bibliometric analysis"

I think this statement refers to the issues I discussed above (see points 2, 3, 6, 9-15). The purpose of the subset analysis is to evaluate the research trends over this period of time in 5-year intervals. In particular, see p20 lines 11-15 and p22 lines 17-21.

32. "evaluation of the top keywords in 5 year intervals showed that the relative contributions of each research area to the total number of papers has remained static, with the largest contribution to the area of epidemiologic aspects of iron deficiency anemia. The citation rate of the top cited papers in this study is high compared to studies on other research areas using similar methodology [11]." The study design, search keywords, and methods are not accepted. Thus, related discussions are not appropriate.

I think this statement refers to the issues I discussed above (see points 2, 3, 6, 9-15).

33. "This study was a bibliometric analysis of the medical literature on iron deficiency anemia published over the last 20 years." The study design, search keywords, and methods are not accepted. Thus, related conclusions are not appropriate.

I think this statement refers to the issues I discussed above (see points 2, 3, 6, 9-15).

34. "Five research hotspots were identified" What are their development trends? It should be in "Trends in iron deficiency anemia research 2001-2020: a bibliometric analysis" There is no conclusion about "Trends in iron deficiency anemia research 2001-2020: a bibliometric analysis"

I think this statement refers to the issues I discussed above (see points 2, 3, 6, 9-15). In addition, see p20 lines 11-15 and p22 lines 17-21.

In closing, I would like to thank the reviewers for their thoughtful critiques, which allowed me to improve my manuscript. I am hopeful that my clarifications have addressed the above concerns. In the revised version of the manuscript, all changes are indicated in RED. If there are any further issues with the manuscript, I would be happy to address them expeditiously.

Sincerely,
John L Frater, MD