Dear Professor Fišter,

Re: Manuscript ID BMJ.2015.030619 entitled "The impact of transfusion thresholds on mortality and cardiovascular events in patients with cardiovascular disease (non-cardiac surgery): A Systematic Review and Meta-analysis"
Thank you for giving us the opportunity to respond to your and the reviewers' comments on the above submitted manuscript. We have carefully considered all of the very helpful comments and a full response is attached. We believe that this is an important review as it is the first to specifically undertake meta-analysis for outcomes in patients with chronic cardiovascular disease, in addition to patients presenting with acute coronary syndrome. Previous guidelines and editorials have advocated greater caution with restrictive transfusion triggers for patients with acute coronary syndrome and chronic cardiovascular disease, but largely based on lack of evidence and the strong physiological rationale that these patient populations are at higher risk of ACS from the combination of atheroma-related flow limitation and anaemia.
We have changed the introduction to highlight the novelty of our research question, especially for providing data to further inform the "uncertainty" and poor evidence highlighted in published guideline recommendations for the patients with cardiovascular disease. We have also changed the title from the original in response to your suggestion. Thank you for considering our work further.

Yours sincerely,

Annemarie Docherty

Comments from Reviewers
Reviewer 1: Patient reviewer
We thank the patient reviewer for his comments, and appreciate that our paper may be more focussed on refining the use of blood transfusions which may be less applicable to a patient reader. We have not made any specific changes to the manuscript based on his comments. We do believe that our findings are of potential interest to the non-medical reader and might inform patients in their discussions about receiving a blood transfusion. A patient discussion of the risk/benefits of blood transfusions is recommended in the recent NICE guidance. The same guidance, which included two lay/patient members in the Guideline Development Group, highlighted the lack of evidence for our research question and made it a research recommendation for future work. We hope we have started to address this evidence gap with our study.

Reviewer: 2
Comments:
This manuscript performs a review and meta-analysis of clinical trials of restrictive and liberal red cell transfusion triggers to determine if the overall favorable outcomes suggesting that restrictive triggers are safe can be shown to be true in patients with cardiovascular disease (CVD). This issue is important since it is not clear from some of the previous large studies or pilot studies that restrictive triggers are safe for patients with cardiovascular disease and whether clinical practice guidelines requires more extensive clinical trials in this area to determine the best transfusion triggers for patients with CVD. Red cell transfusion guidelines have been based upon a number of clinical trials reviewed by the authors but the application of these data for patients with CVD remains unclear; CVD is one of the remaining areas of concern along with patients undergoing neurovascular procedures and patients with hematologic malignancies. The study was carefully performed by authors with experience in this type of analysis and the results are presented in adequate detail. The accompanying protocol is clear and the paper appears to follow the plan expressed in the protocol. Although the study was carefully performed and is well documented in the submitted manuscript, there are several areas that could be addressed to improve the presentation:
Thank you for these positive comments.
1) As stated by the authors, the definition of CVD is broad and was not consistent in the studies that were reviewed. It was difficult for this reviewer to determine how the decision was made to include studies which categorized patients with a history of CVD and whether these inclusions were consistent. Although the inclusion of ischemic cardiac disease is relatively straightforward, other patients with TIA, stroke, pulmonary edema, or peripheral vascular disease were included in some but not all studies. It would be helpful for the manuscript to provide a specific statement of how they determined which studies had rigorous definitions of CVD to include in the meta-analysis. It would also be helpful for the authors to identify the characteristics of patients with CVD they included so that further studies can be directed to these patients and guidelines can explicitly define the population that they are addressing.
Thank you for your recommendations regarding the definition of cardiovascular disease. We have now included the definition from the protocol in our methods section (p5, lines 119-124), and have included a table (E1) of each author's definition for cardiovascular disease to maximise clarity.

2) The definition of who had a cardiac event during the reported clinical trials is also a concern. The definitions of an ischemic event (AMI, ACS) are clear and the results document that a restrictive transfusion trigger may result in a higher risk of ischemic events. The inclusion of acute pulmonary edema as a cardiovascular event is not as convincing. Some of these reported events may be due to fluid overload from more liberal transfusion practices and not attributable to CVD specifically. The manuscript documents no clear signal about APE as an outcome associated with liberal and restrictive transfusion. Perhaps the manuscript should focus on ACS outcomes alone and not consider APE where causation and relation to CVD is not as clear.
Thank you for your comments regarding acute pulmonary oedema (APO). We agree that there are multiple potential causes for APO, including fluid overload. We also recognise that Transfusion Associated Circulatory Overload (TACO) is now the most commonly associated transfusion complication, and manifests as APO. We believed it important to report both outcomes, but recognise that the mechanisms are different and the effects could be in different directions. Specifically, fluid overload is a potentially important risk from more liberal transfusion practices. We have made a clearer acknowledgement of the importance of separating these outcomes in the discussion, and the difference in the evidence quality we found in the study (p16, lines 393-398)

3) The exclusion of children and neonates where coronary artery disease (CAD) is uncommon is well supported. In

elderly patients without diagnostic criteria for CAD, the incidence of silent and yet undiagnosed CAD is probably higher. Did the authors look at patient age to determine if older patients who are more likely to have silent CAD had different event rates and more ACS events with restrictive or liberal transfusion practices?
Thank you for this comment, we agree that older patients may be at higher risk of undiagnosed coronary artery disease. However, our included trials did not stratify their data by patient age, and we were unable to extract data for this important group from the studies. This would certainly be an important group to study in the future.

4) The abstract for the paper concludes that there is a need for further research into best practice. The conclusion in the DISCUSSION, however, states the restrictive transfusion practice may not be as safe and recommends "higher transfusion threshold for patients with acute and chronic CVD until adequately powered high quality randomized trials" are performed. The abstract conclusion and the discussion conclusion should be consistent. If the authors truly believe that a change in transfusion practice is justified before clinical trials are performed, they should state their view explicitly. They should also recommend what trigger they would support. They should recognize, however, that this type of statement in the BMJ may make it difficult to perform the clinical trials they advocate, since they imply that equipoise does not exist. If practice changes are advocated and adopted, IRBs may not allow the studies that would be needed. The authors should rethink their conclusions and determine which position they are advocating and defending.
Thank you for this important point. We agree it is the key message from our study. We believe that we have provided evidence that a restrictive transfusion threshold is associated with an increased risk of ACS, but shown that evidence for mortality and other important outcomes such as length of stay, quality of life, and cost-effectiveness is inconclusive. We believe that more research is needed, but that caution should be used in this population to decrease the potential for harm, especially given the "push" to implement restrictive transfusion triggers (near 70g/l) widely. After careful consideration we have chosen the following conclusion:
"In conclusion, this review of available evidence suggests that for anaemic patients with cardiovascular disease the use of restrictive haemoglobin thresholds for blood transfusion (typically 70-80g/l) is associated with higher rates of ACS than more liberal thresholds (typically 90-100g/l). No effects on mortality or other important outcomes were demonstrated. The currently available quality of evidence for all outcomes is low. These data support the use of a more liberal transfusion threshold (greater than 80g/l) for patients with both acute and chronic cardiovascular disease, until adequately powered high quality randomised trials have been undertaken in this patient population."
This is consistent with the evidence we reviewed and provides a clear message to readers, whilst emphasising the importance of further research in this patient population. We have re-written the conclusion to the abstract (pages 2-3; lines 49-53, as above), and the discussion (page 16; line 399-406). We include additional text in the discussion for the rationale for suggesting maintaining a haemoglobin >80g/l based on the haemoglobin values reported in the restrictive groups of the included RCTs (page 15; pages 379-384).

5) It would be helpful to clinicians reading this paper for the authors to put in perspective how often an ACS event might occur in a patient transfused with a restrictive trigger and how often it might be prevented by a more liberal transfusion trigger. The readership would benefit from a more explicit explanation of the public health benefits or adverse consequences of their findings
We thank you for your advice in making our paper more helpful to clinicians, and we have therefore included the number of patients with ACS/hundred patients in restrictive and liberal transfusion threshold arms, and have included a number needed to prevent ACS (p12, lines 294-297). In addition to this, we have commented on the prevalence of CVD (p4, line 75). We include some additional discussion further highlighting this message from the data (page 15; lines 375-76)

Reviewer: 3

The review is timely, important and will be helpful to a broad range of clinicians and researchers. It is thorough, meeting all methodological requirements for a systematic review, as well as being well written and easy to follow. The authors make a number of important points, including the limitations of the evidence available for review, and the different definitions used for a range of events. The also highlighted that the duration of the intervention from randomisation varied considerably from only 14 days to one year, but was mostly quite short, so the longer-term consequences of these transfusion strategies are essentially unknown. The authors identify important outcomes such as quality of life and cost-effectiveness that should be included in future clinical trials in this area.
Thank you for these positive comments.

SPECIFIC COMMENTS
The scientific question is clear and well defined. The methods are robust, the references up to date, and the conclusions are appropriate.
My comments are all minor.
Methods
Page 6, lines 45-50: The sentence commencing "Data on cardiovascular events…" is somewhat confusing, perhaps because of the parentheses – are all types of cardiovascular events included in the review captured simply under the term "ACS"?
Thank you for this comment, which we agree is confusing. We hope that we have clarified this (p7, lines 161-163).

Page 8, line 17: "However, recent guidelines (18), which have highlighted the need for further research in this area, have included patient representatives." This is a true statement, but it does not add anything to the preceding statement that "There was no direct patient involvement in this systematic review." Suggest just delete it.
Thank you for this observation, we have deleted this second sentence.

Acute coronary syndrome is abbreviated as ACS but not used consistently thereafter (e.g. written in full on page 11, line 23).
Thank you, we have changed to "ACS" after the first use of the term.
Could probably abbreviate the term "red blood cells" early and use throughout to save a few words.
Thank you, we have changed to "RBC" after the first use of the term

Reviewer: 4
Comments:
This is a comprehensive review and metaanalysis of transfusion thresholds in patients with cardiovascular disease. Protocol was clear and fully executed. Conclusion was supported by the results and there was an objective assessment of the limitations of the evidence as well as the review.
Response to comments from the committee:
* Most (about 2000 people of the total 3000) of the data here are from one study - Carson 2011 NEJM, and the headline results of the current article repeat what this paper found.
Also, you write that "The 2012 Cochrane review recommended the use of a restrictive transfusion trigger, but suggested caution in patients from high-risk groups such as acute coronary syndrome".
Can you convince us that your study adds in some very important way to these previous papers, so we should prioritise it for publication in the BMJ?
As an additional point, we felt that novelty should have been better discussed in the paper, in relation to these two and possibly other publications (such as your BMJ paper published last year).

Thank you for highlighting these important points. We believe that our paper is significantly different from the Carson 2011 trial, and importantly our conclusions and recommendations are different based on the systematic review and meta-analysis of available data.
Our paper is the first to specifically undertake meta-analysis for outcomes in patients with chronic cardiovascular disease, in addition to patients presenting with acute coronary syndrome. Previous guidelines and editorials have advocated greater caution with restrictive transfusion triggers for patients with acute coronary syndrome and chronic cardiovascular disease, but largely based on lack of evidence and the strong physiological rationale that these patient populations are at higher risk of ACS from the combination of atheroma-related flow limitation and anaemia.
Carson found a non-significant increase in the risk of ACS [RR for ACS 1.65 (0.99, 1.74)]. We have added his excellent study to the others in this field, and found that the effect estimate is statistically significant, with little statistical heterogeneity, and a similar clinically important risk difference [RR 1.71, 95% CI 1.11 to 2.65, P=0.01, I2= 0%]. We removed the Carson trial in a sensitivity analysis and found that there was still a significant increased risk of ACS in the remaining studies even though they were smaller [RR 2.07 (1.02, 4.23)]. Importantly, we have added other clinical populations with chronic cardiovascular disease (notably critical care) to the Carson population (fractured neck of femur). We think this relevant given the differing duration of exposure to anaemia and risk of death between these populations.
We have changed the introduction to highlight the novelty of our research question, especially for providing data to further inform the "uncertainty" and poor evidence highlighted in published guideline recommendations for the patients with cardiovascular disease.

It was good to see a systematic review registered in PROSPERO, however the secondary outcomes mentioned there don't seem to be presented in the paper. As with trials, we believe you should report all prespecified outcomes OR clearly state which outcomes will be reported elsewhere.
Our protocol stated the following secondary outcomes:
Our primary outcome was mortality at 30 days. We also extracted mortality data at 60 days, Critical Care and hospital mortality, and other mortality defined by authors.
Data on cardiovascular events were categorised as Acute Coronary Syndrome (ACS), Acute Pulmonary Oedema (APO), peripheral ischaemia and thrombotic events wherever possible. The category of ACS included myocardial infarction (MI), acute coronary syndrome, and cardiac arrest.
Measures of general morbidity were use of packed red blood cells, adverse transfusion reactions, incidence of in-hospital infections, measures of organ dysfunction, duration of ICU/hospital stay, invasive ventilation, haemodynamic support, renal support.
We have added these to our methods section (p7, lines 164-166), and have mentioned all outcomes in the results section, with a summary table in the on-line supplement (Tables E2, E3)

Although the individual studies looked at various thresholds, your paper is effectively looking at liberal vs restrictive red cell transfusion policies in people with cardiovascular disease undergoing non-cardiac surgery. We felt the title could more clearly reflect that, mention the two policies better than thresholds. Also, we don't see the need for parentheses.
Thank you for your advice regarding clarifying our title. We have changed to using the term "strategies" as the preferred term, as we think this reflects what was done in the trials. Our review encompasses critical care, coronary care, and upper GI bleeding in addition to surgery, and we are keen that our title implies non-surgical settings. We suggest amending to:
"The impact of restrictive versus liberal transfusion strategies on patient outcomes in patients with cardiovascular disease excluding those undergoing cardiac surgery: A Systematic Review and Meta-analysis"

Missing are the data sharing statement, and information on ethics committee consideration. Please include in the revision, and see below for a full list of required statements.
We have included this statement.

1. Response to reviewer comments Docherty.docx PDF HTML