Is patient blood management cost-effective? Response to *Br J Anaesth* 2021; 126: e7–9

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Editor—Trentino and colleagues[1] question whether our network meta-analysis[2] finding that no trial of patient blood management has shown cost-effectiveness was an accurate representation of the data. We assessed the cost-effectiveness of patient blood management interventions by updating the 2015 National Institute for Clinical and Healthcare Excellence (NICE, UK) guideline on blood transfusion review of studies evaluating the cost-effectiveness of patient blood management interventions.[3] Our searches identified only one trial[4] that reported the cost-effectiveness of a patient blood management intervention as assessed by incremental cost-effectiveness ratio (ICER) or cost/quality-adjusted life-years (QALYs). This trial was cited correctly in the manuscript (in reference 18,[5] which describes the health economic analysis in great detail, and in reference 29,[6] the primary manuscript). Both reports concluded that there was 'no clear difference in the cost-effectiveness of restrictive and liberal thresholds for red blood cell transfusion after cardiac surgery'.

In their second point, the authors are correct in drawing attention to the limitations of meta-analyses that include multiple small trials of variable quality. To address this, we performed sensitivity analyses that excluded trials at high risk of bias, and trials at risk of allocation concealment bias (the most common form of bias in small poorly conducted trials). The results of the sensitivity analyses were consistent with the main results, further supporting our conclusions. Our review also identified many well-conducted multicentre RCTs in patient blood management. No high-quality trial refuted our findings.

The third point raised by Trentino and colleagues highlights potential discrepancies in the costs of red blood cell transfusions estimated from their work[6–8] and those estimated in the Transfusion Indication Threshold Reduction (TITRe2) trial.[4,5] Non-randomised studies cannot adequately address the competing risks of non-transfusion or patient blood management interventions. In contrast, the health economic analysis of the TITRe2 randomised trial measured these factors.[4,5] Moreover, the reporting of the health economic analysis was pre-specified, transparent, rigorous, undertaken by an internationally leading health economics team, and published in a leading peer-reviewed journal.

Trentino and colleagues are correct in that 32 of 38 RCTs evaluating costs showed cost reductions attributable to patient blood management. However, it is incorrect to suggest that this equates to cost-effectiveness, for the reasons alluded to above. In our analysis, it was therefore accurate to state that no trial has shown patient blood management to be cost-effective.

Javidroozi and colleagues[9] are incorrect in suggesting that we have shown a reduction in hospital or ICU length of stay attributable to patient blood management. We showed high heterogeneity for these two outcomes, and publication bias for hospital length of stay. This means that the assumptions for meta-analysis estimates are not valid and point estimates are unlikely to be accurate.

The associations between transfusion and adverse outcome in observational analyses are confounded by indication bias, lead-time bias, reverse causality, and other unmeasured variables. In contrast, we used contemporary Cochrane methodology to summarise evidence from RCTs, the most effective technique to identify causality. We showed no treatment effect of patient blood management on clinical outcomes with no or low heterogeneity despite >30% reduction in transfusion across almost 400 trials. It is important to point out that there is no single high-quality trial that has demonstrated harm from red cell transfusion. We can, therefore, conclude that there is no causal association between transfusion and adverse outcomes.

The authors correctly highlight the limitations of underpowered studies when assessing outcomes with low incidence (e.g. mortality). The design of meta-analyses aims to address this shortcoming, despite the limitations of the aggregate data approach. In this meta-analysis, the number of patients included in assessing differences in mortality was 26 766, and the number of included RCTs was the largest to date. Also, our review showed no benefit for other important and more frequent clinical outcomes: renal failure, acute brain injury, myocardial infarction, and infection, underlining the consistency of our findings.

We agree that the individual participant data (IPD) approach may provide further important insights into this research question,[10] but politely disagree that this invalidates our findings. We used contemporary search methods and Cochrane methodology, and implemented a pre-specified published protocol to identify 393 RCTs. Along with the consistency of the results, these metrics of quality attest to the validity of the findings.

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Finally, Javidroozi and colleagues[9] highlight statistical and clinical heterogeneity as limiting factors in our analyses. We performed multiple subgroup and sensitivity analyses to test the robustness of the primary analyses for the clinical setting, disease type, comorbidities, anaemia at baseline, the target of intervention, and trial quality. We showed that none of these factors contributed significantly to the analysis and heterogeneity of clinical outcomes. In fact, the most striking feature of the analysis was the consistent lack of any treatment effect for patient blood management on clinical outcomes.

The authors also identify the limitations of network meta-analyses to personalised medicine. We highlighted these points in the discussion. This does not, however, explain the observation that no single intervention had important clinical benefits.

In summary, the authors of these two letters do not, in our view, present evidence that undermines the validity of our findings. We, therefore, consider the title and manuscript to be an accurate representation of the available evidence.

Declarations of interest

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Is patient blood management cost-effective? Comment on *Br J Anaesth* 2021; 126: 149–56

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