Austin Health

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Dear Chief Editor

ESPS Manuscript NO: 03194307

Manuscript Type: Review

Thank you for considering the above manuscript for publication in the *World Journal of Critical Care Medicine.*

We appreciate the detailed comments provided by the 3 expert reviewers. Please find below a detailed response addressing each comment raised.

Editorial comments

1. **Editorial comment:** Please put the reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. Please check across the text. **Authors reply:** This has been corrected throughout the manuscript.

Reviewer 00506051

Thank you for your detailed comments and for your time in reviewing our manuscript. Please find below an itemized reply to each comment raised.

1. **Reviewer comment:** It is not clear whether manuscript was invited or already published or rejected for publication? Why are authors stating: "This article is an open-access article, which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the

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Authors reply: The manuscript is an invited manuscript. The statement above was inserted following the instructions for authors on the Journals website. The article has not been previous peer-reviewed by any external reviewers. Your expert comments are therefore most valued and have both enhanced and improved the manuscript.

2. **Reviewer comment:** A paragraph describing color changes of the PL 148 and propofol should be rephrased. Why should anyone "draw conclusions based on visual inspection or turbidity testing alone"?

Authors reply: Thank you for this important comment. Under the section "Compatibility with other intravenous medications", the section has been revised and clarified. The section now reads: *"The physical compatibility of PL 148 with medications commonly used in the operating theatre and critical care settings has been investigated. PL 148 was tested with 87 drugs for physical compatibility immediately on mixing, 1 hour and 4 hours after mixing. Compatibility was determined by visual examination performed under normal, diffuse fluorescent laboratory light. Turbidity was measured under high-intensity, mono-directional light using a portable turbidimeter. On mixing, visual appearance changes occurred with amiodarone, cyclosporine, propofol and mycophenolate. An increase in turbidity was observed with pantoprazole and phenytoin, amiodarone, cyclosporine, propofol and mycophenolate.*

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3. **Reviewer comment:** Reference for sentence "More specific to PL 148, due to its alkalinizing effects, the renal elimination of acidic drugs such as aspirin and barbiturates, or drugs such as lithium, may increase" is missing.

Authors reply: Thank you for pointing out this omission. This has been corrected.

4. **Reviewer comment:** In the Table 2 a statistical significance should be presented rather than endpoints of the findings. Otherwise, the manuscript is appropriate for publishing

Authors reply: Thank you for this excellent comment. The significance levels (p-values) have now been included in Table 2. Where the p-value was not stated in the original published paper we have stated "*p value: not stated"*.

Reviewer 00526025

Thank you for your detailed comments and for your time in reviewing our manuscript. Please find below an itemized reply to each comment raised.

1. **Reviewer comment: General comments:** Readers could understand the clinical results of Plasma-Lyte 148 more easily if the authors would add numbers of patients, death rates, if applicable, of each study the authors cited in the text.

Authors reply: Thank you for this very valuable comment. The numbers of patients for all clinical trials examining the effects of Plasmalyte have been articulated in Table 2. We

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have been advised not to repeat what is already summarised in Tabular Form. If the Reviewer or Editorial board would like this further revised, we would be most happy to make these changes.

2. **Reviewer comment:** Readers would appreciate it if the authors would revise Table 2 in order of citation in the text.

Authors reply: Thank you for this valuable suggestion. The order of citation in Table 2 followed a chronological sequence. We have now changed this to reflect the order of citation in the text.

3. **Reviewer comment:** Addition of the first author's name in Table 2 would greatly help readers clearly understand what the authors are describing.

Authors reply: Thank you for this very valuable suggestion. The author's first name has now been included in the Table 2.

4. **Reviewer comment:** Abbreviations in Tables two need explanation.

Authors reply: This has been amended. Thank you.

5. **Reviewer comment: Specific comment:** Page 16, line 3 from the bottom: "And" between lower "and" prothrombin times should be deleted. END

Authors reply: Thank you for highlighting this typographical error that has now been corrected.

Reviewer 02488945

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Thank you for your detailed comments and for your time in reviewing our manuscript. Please find below an itemized reply to each comment raised.

1. **Reviewer comment:** The **second page** of the article says that it is an open access article and is fully peer reviewed. Does this mean that it is published elsewhere as an open access article? If not, and is fully peer reviewed then why am I re-reviewing it?

Authors reply: As commented by Reviewer 00506051 above, the manuscript is an invited manuscript. The statement above was inserted following the instructions for authors on the Journals website. The article has *not* been previous peer-reviewed by any external reviewers. Your expert comments are therefore most valued and have both enhanced and improved the manuscript.

2. **Reviewer comment: Abstract**: Last sentence has a typographical error: Critically illness: should be critical illness or critically ill patients

Authors reply: Thank you for highlighting this typographical error that has now been corrected.

3. **Reviewer comment: Page 4**: **© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved… and … Weinberg L, Collins N, Van Mourik K, Tan C, Bellomo R. Plasma-Lyte 148: A Clinical Review**.** *World J Crit Care Med* 2016…so is the article already published?

Authors reply: As commented above, the manuscript is an invited manuscript. The statement above was inserted

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following the instructions for authors on the Journals website. The article has not been previous peer-reviewed by any external reviewers. Your expert comments are therefore most valued and have both enhanced and improved the manuscript.

4. **Reviewer comment: Key words**: Please omit anesthesia and replace it with perioperative medicine. Also, Intravenous should be replaced with IV fluids

Authors reply: This has been corrected.

5. **Reviewer comment:** In the **Description** section, Mg levels are mentioned in mEq while later in the script the authors have changed it to mmol. Same for K. Please stick to the same unit throughout the script.

Authors reply: Thank you for this important and valuable comment. All units have been change to reflect the same format throughout the manuscript.

6. **Reviewer comment:** The authors mention that the pH of plasma lyte 148 is 7.4. (In the table it is 4 to 8) But the drug company which manufactures the solution, Baxter, says that the pH ranges from 4 to 6.4. (http://www.baxterhealthcare.com.au/downloads/healthcare_professionals/cmi_pi/plasmalyte148_pi.pdf)

Authors reply: Thank you for this very important and insightful comment. The formulation "Plasma-Lyte 148 (approximate pH 7.4)" is the only Plasma-Lyte formulation available in Australia and New Zealand. The formulation is approved by the Australian Therapeutics Goods Administration and registered in both Australia (AUST 231424 and 48512) and New Zealand. The pH of Plasma-Lyte 148 is adjusted with sodium hydroxide and reported as approximately 7.4, however depending on country of

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manufacture, the pH ranges from 6.5 to 8.0.This has been clarified in the manuscript. In addition we have also clarified this in Table 1.

7. **Reviewer comment:** For **precautions**: The described precautions are the same for all IV fluid and hence there is no need to mention them as this is just a review and not drug information leaflet

Authors reply: Thank you for this very valuable comment. We have now deleted the paragraph stating "*Common to all fluid solutions, the administration of PL 148 in large volumes can result in fluid and/or solute overload with consequent sequelae of congestive cardiac failure, pulmonary congestion, dilution of serum electrolyte concentrations, and acid-base imbalances. Plasma-Lyte 148 should therefore be administered cautiously to patients who are predisposed to sodium retention, fluid overload and oedema*"

8. **Reviewer comment: Compatibility** section: second sentence needs re-phrasing. The authors mention that visual appearance with propofol changes. Can you please describe the changes? Later in the same paragraph it is mentioned that …since propofol is 'milk-white' (should read "milky-white") it is difficult to draw conclusions. Please mention clearly about interaction with propofol since this is extremely important for all anesthetists.

Authors reply: Thank you for this important comment. Accordingly we have completely revised the section on compatibility. This now reads *"The physical compatibility of PL 148 with medications commonly used in the operating theatre and critical care settings has been investigated. PL 148 was tested with 87 drugs for physical compatibility*

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immediately on mixing, 1 hour and 4 hours after mixing. Compatibility was determined by visual examination performed under normal, diffuse fluorescent laboratory light. Turbidity was measured under high-intensity, mono-directional light using a portable turbidimeter. On mixing, visual appearance changes occurred with amiodarone, cyclosporine, propofol and mycophenolate. An increase in turbidity was observed with pantoprazole and phenytoin, amiodarone, cyclosporine, propofol and mycophenolate."

9. **Reviewer comment: Drug interaction**: Are there any references and is there any dose adjustment recommended for interacting drugs?

Authors reply: This is a very important comment. We have critically reviewed the literature once again and made direct contact with Baxter Healthcare to seek clarification regarding this question. At present there is insufficient evidence for any dose adjustment with interacting drugs. This has been included in the revised manuscript.

10. **Reviewer comment: Laboratory test interaction**: For Glutamate: Were the manufacturing processes different in the study by Spriet at al. and the previous four studies mentioned in the article which reported false positive galactomannan test results.

Authors reply: This is a very important comment. We have stated in the manuscript that with contemporary sophisticated manufacturing processes, Plasma-Lyte 148 does not result in false-positive galactomannan test results. The exact manufacturing processes are propriety.

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11. **Reviewer comment: Osmolality**: the script says that it is 271 mOsm (Different value mentioned in the table) while the manufacturing company, Baxter says that is approx. 291 mOsm (http://www.baxterhealthcare.com.au/downloads/healthcare_professionals/cmi_pi/plasmalyte148_pi.pdf)

Authors reply: With the current formulation of Plasma-Lyte 148 in Australia and New Zealand, the approximate osmolality is 271 mOsmol/kg H20 as determined by an osmometer using the technique of freezing-point depression. In other countries, the stated osmolality is approximately 291 mOsmol/kg H20. This has been clarified in the text and in Table 1.

12. **Reviewer comment: Other electrolytes**: Acronym PL 148: Please mention acronym for each word when used first time in the script in bracket and then mention only the acronym. The full name Plama Lyte 148 should not be used in this paragraph, use only PL 148 throughout the script.

Authors reply: Thank you for this comment. This has been corrected.

13. **Reviewer comment: Strong ion difference**: Please mention acronym SID in bracket first and then use it in the paragraph.

Authors reply: Thank you for this important comment. This has been corrected.

14. **Reviewer comment: Strong ion difference**: 5th line: ion-different…should be ion-difference

Authors reply: Thank you for this important comment. This has been corrected.

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15. **Reviewer comment: Renal transplantation**: (Transplant?): second last sentence has a typographical error, please rephrase. (The incidence of hyperkalemia was not statistically different groups.)

Authors reply: Thank you for this important comment. This has been corrected.

16. **Reviewer comment:** Are there any studies **comparing Sterofundin iso and Plasma Lyte 148**; since these are very similar.

Authors reply: Thank you for this interesting question. We agree that Sterofundin is similar to Plasma-Lyte 148, but has a very different and unique physiochemical profile. Sterofundin is a very hyperchloremic solution (chloride content 127 mmol/L) vs. Plasma-lyte (chloride content 98 mmol/L). As already discussed in the manuscript, there is emerging data suggesting a strong association with hyperchloremia and adverse renal outcomes. Second, the effective strong ion difference of Sterofundin is 25.5 mequ/L compared with Plasma-Lyte, which has a SID of 50. Comparatively, Plasmalyte is therefore a very alkalinizing solution. Unlike Sterofundin, Plasma-Lyte 148 is calcium free and therefore compatible with blood and blood components. The purpose of our review was to provide critical analyses of Plasma-Lyte 148, and we have not expanded on the specific physiochemical properties in detail of the any of the other commonly available crystalloids. We agree with the Reviewer that the reader should be informed that there are “similar” crystalloids commercially available, and have included the physiochemical profile of Sterofundin in Table 1 for comparison.

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17. **Reviewer comment:** It would be nice to have one table mentioning specific indications (like renal transplant etc), interactions, cautions and contraindications for the readers for a quick reference.

Authors reply: Whilst we agree with the Reviewer that such a Table would be a valuable addition to the manuscript, we are also mindful that, at the present time, there is insufficient data from the literature to advocate for the use of any one crystalloid solution over another. We hope that our review allows the reader to make a more informed decision when choosing crystalloid solutions as fluid therapy; clinicians should have a fundamental understanding of each fluid's specific physiological properties. Our review discusses therefore is restricted to the benefits and limitations of Plasma-Lyte 148 as a choice of solution for fluid intervention in critically illness, surgery and perioperative medicine.

18. **Reviewer comment:** The summary of clinical trials is well tabulated.

Authors reply: Thank you for this positive comment.

19. **Reviewer comment:** The last part of **conclusion** should be rephrased as: *The ideal approach for perioperative fluid therapy should therefore always be individualized:*
    - *Qualitatively: Fluid with suitable physicochemical composition individualized to patient's physiological state and specific type of surgery*
    - *Quantitatively: the right amount of fluid at the right time and at the right rate*

Authors reply: Thank you for this excellent suggestion, which we have now incorporated in to the conclusion of the manuscript.

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Once again, I would like to personally thank the Reviewers for the time taking in providing valuable comments for this manuscript. I hope our detailed responses are satisfactory. We would be very happy to make further revisions if needed.

With warm regards,

Sincerely,

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