Peer Review File

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Reviewer A

Overall, I think this is an interesting literature review and your main thesis, that WWLST after the baby is initially resuscitated contributes to mortality outcomes, is important for neonatologists to recognize. There are quite a few amendments that you could make in order to make this a publishable paper.

General Comments:

1- This is a narrative/literature review, not an original article (as entered)

Reply 1: Have changed the article type to literature review

Changes in the text: "Article Type: Narrative Review"

2- When using the term "outcomes" I would clarify by specifying mortality or morbidity.

Reply 2: while the bulk of the review focuses on mortality, some comment is made about morbidity as well

Changes in the text: "The morbidity and mortality of infants born extremely preterm varies substantially across networks, within countries and throughout the globe." As well as other locations throughout the text where we have specified this further.

3- I would take out the words that comment on what you are reporting. For example, in line 90, "positively" does not add to the report but distracts by the judgment.

Reply 3: Agreed, we have made efforts to remove these from the text.

Changes in the text: Removal or substitution of these terms form throughout the text.

4- The paper would read easier by keeping the tenses of the verbs consistent.

Reply 4: Thank you for drawing our attention to this.

Changes in the text: An effort has been made to unify tenses where possible throughout the text.

5- The Background section is very long. I would condense some of these paragraphs and choose what's most important.

Reply 5: The background section has been re-worked to refine the rationale and focus more specifically on the content of the literature review.

Changes in the text: In the background section we have deleted the finer details about studies which do not relate to the rationale and have expanded sections suggested by yourself and other reviewers. We have rearranged other paragraphs to form a more logical narrative.

Specific Comments:

1- L18-19: Please clarify whether outcomes are for morbidity, mortality, or both.

Reply 1: Thank you for drawing our attention to this.
Changes in the text: An effort has been made to unify tenses where possible throughout the text.

2- L19-21: I find the term "front-end" confusing and recommend describing the concept more clearly than the explanation in these lines.
Reply 2: We have amended as suggested
Changes in the text: "Most of the literature tends to focus on the management at birth and choices around active resuscitation of extremely preterm infants"

3- L23-24: Since you did not actually do a study but a literature review, I don't think a hypothesis is appropriate here. Maybe put in a sentence such as "Outcomes, in terms of both mortality and morbidity, do not just depend on early life decisions and management, but also later life decisions to WWLST."
Reply 3: We have amended as suggested
Changes in the text: "As such, our objective in this review was to explore whether end of life decisions also contribute to variations in the morbidity and mortality of periviable infants."

4-L51 Risks have not been discussed in previous sentences. Maybe us the term "effects."
Reply 4: We have amended as suggested
Changes in the text: "These effects are particularly noted at the limits of viability, however outcomes are improving."

5-L55-56: Why define periviable birth as 20-25 6/7 weeks when this differs from the literature? Clinically, periviable births are <24 weeks.
Reply 5: We have re-visited the literature and have presented the point from a different angle. While it is often cited that periviable infants are <26 weeks the actual period of contention and differing management rated is in th "grey zone"
Changes in the text: "Periviable birth is defined as those births occurring from gestational ages (GAs) 20+0 to 25+6 weeks.(7-9) However, over the last decade with improving technology and management of periviable infants there has been a shift to increased resuscitation in younger gestations, creating the "grey zone" at 22 to 24 weeks' gestational age.(9-11)"

6-L68-69: Instead of listing references, I recommend either putting references at the end of the sentence or describing the studies.
Reply 6: We have described the studies in more detail, however if this proves to be too long and detailed for the background section we could condense it back down again.
Changes in the text: See paragraph 2 of the background section

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7- L73-75: This is the first reference to a table in the paper, so should be Table 1. This table does not seem to highlight key studies. A better explanation of what this table represents either under the table or in the text would be helpful.

Reply 7: Apologies, the tables have now all been re-numbered correctly
Changes in the text: We have also added a paragraph describing the table.
"This table shows variable survival statistics reported by studies over the last 15 years. Importantly, there are variable definitions of survival based on the denominator (number of infants included based on total births, live births, actively managed births or admissions to the NICU). Most of the data spans the last two decades but not more recent years. Further, the length of assessment time also varies from discharge through to young adulthood. Survival was also not always assessed at each gestational week in these studies. Generally, survival increased with increasing gestational age. NB: the author recognises a more comprehensive list might include the recent annual reports of each neonatal research network however this was not included as these are both difficult to access and not the primary focus of the review."

8-L87-88: This sentence is confusing. Please rewrite.
Reply 8: We have removed this section of the background as part of improving relevance and readability
Changes in the text: Removed from the text

9-L91-94: This is a long, confusing sentence. How is this an ethical dilemma? Is this important for background material? I recommend either fleshing it out more or exclusing it.
Reply 9: We have excluded this sentence
Changes in the text: Sentence deleted

10-L100-101: Again, I suggest that you don't have a hypothesis for a literature review.
Reply 10: We have re-worded this sentence
Changes in the text: "Thus, we must investigate whether WWLST might be a crucial source of outcome variation in periviable infants."

11-Methods: What did you do with the papers once you had them? Did one author review? All authors reviewed and compared?
Reply 11: As this was not a systematic review, the studies were mainly chosen to be included by one reviewer as described below
Changes in the text: "One author, I. Galloway independently selected the literature to include but would consult the other authors if the study's importance or relevance was unclear."

12- Main Body: I might change this title to "Literature Review"
Reply 12: We have amended as suggested
Changes in the text: "3. Literature Review"

13- L133-136: Please rewrite for clarity.
Reply 13: We have amended as suggested
Changes in the text: "This may be a better recognition of medical futility,28 or potentially because neonatologists are increasingly routinely resuscitating infants

of lower gestational ages at birth who are at greater risk of subsequent deterioration."

14-L144-147: These factors were associated with discussions of WWLST, not WWLST.
Reply 14: We have reviewed the literature and clarified this claim
Changes in the text: "Factors that have been associated with discussions about WWLST include being male, white ethnicity, <24 weeks gestation, small for gestational age, congenital malformations/syndromes, early-onset sepsis, severe brain injury and necrotising enterocolitis,(25, 26)"

15-L148-149: These are most likely to be withheld or withdrawn (not just withdrawn)
Reply 15: We have amended as suggested
Changes in the text: "Life sustaining treatment is also more likely to be withheld or withdrawn in white infants than in Black or Hispanic infants"

16-L163-164: Parents and neos agree about what?
Reply 16: Changes in text as below
Changes in the text: "While parents and neonatologist usually agree on when WWLST might be indicated, this is not always the case."

17-L165-166: The results of James et al should also be quoted in this sentence.
Reply 17: Thank you for drawing our attention to this
Changes in the text: James et al has also now been cited in this sentence.

18-L165-169: In both sentences, "withdrawing care" should be changed to withdrawing life-sustaining treatment or transitioning to comfort care. We should not withdraw care.
Reply 18: Thank you we have amended this wording
Changes in the text: "However, up to three-quarters of parents eventually withdraw or limit LST after discussions about WWLST.25, 33"

19-L172: 24% is not a small portion.
Reply 19: Agreed
Changes in the text: "About one-quarter (22-24%) of parents decide to continue life sustaining care following WWLST discussions.25, 33"

20-L173: "Unfortunately" seems quite subjective. I recommend removing it.
Reply 20: Thank you for drawing our attention to this
Changes in the text: Deleted from the sentence

21-L173-175: Though many of these patients who had discussion but not WWLST had severe disabilities, only about 50% had severe impairment. One would have to question whether this is accurate clinical judgment for withdrawing life-support for infants that will have mild to moderate impairment (or 10%

unimpaired infants). I suggest either taking the comment out altogether or making a point of the potential inappropriateness of the clinical judgment for some babies.
Reply 21: This question has now been addressed in the amended paragraph. It is an important point to recognize – that there is a spectrum of outcomes that could be possible and we may not yet have tools or judgment accurate enough to predict this with little uncertainty. We have re-written a large part of this paragraph to hopefully reflect this a little more.
Changes in the text: Paragraph 2 in "Outcomes after WWLST" has been re-worked with more evidence and discussion around this

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22-L177-179: For completeness, I recommend including James et al's results where severe neurodevelopmental disability was not as frequent for WWLST survivors. In part, the patients may have been different (Pal et al included primarily patients with severe HIE and James et al included ELBW infants). This could be discussed. Both sets of results (including the patient populations should be discussed with parents, not just the one result of Pal et al.
Reply 22: We have reviewed the study and cannot find the results you are referencing above. Table III of James et al. shows survivors with a WWLST discussion were much more likely than those without to have neurodevelopmental disability.
Changes in the text: We have included James et al.'s findings in this paragraph

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23-L182: I suggest to change to "...withholding or withdrawing life-sustaining treatment or redirecting care."
Reply 23: This is better wording
Changes in the text: "Countries vary widely in thresholds and reasons for WWLST.29, 44"

24-L188: spelling should be "Dworetz"
Reply 24: Thank you for drawing our attention to this
Changes in the text: "This was particularly well documented by Dworetz et al."

25-L196: I recommend taking out this subheading and leaving under the previous subheading.
Reply 25: Agreed
Changes in the text: Subheading removed

26-L235 "started" not "stared"
Reply 26: Thank you for drawing our attention to this
Changes in the text: we have corrected the typo

27-L249-271: I would recommend reworking this paragraph. The listing of guidelines and commentaries regarding WWLST is confusing and not complete (for example, American Academy of Pediatrics guidelines were not included). You mention that none of the guidelines listed are specific to WWLST in the periviable population. Then why list them? If you do use them, I recommend describing what

they recommend instead of being more vague. I also suggest stating specifically that the recommendations for shared decision making must reside within guidelines for WWLST.

Reply 27: The paragraph has been expanded to describe the guidelines more clearly and to summarise their recommendations for shared decision making. The point of the paragraph is to highlight that no guideline truly covers this population and that the guidelines are more values and process based. The American Academy of Paediatrics guideline was already included if you refer to Table 4.

Changes in the text: Please see paragraph 1 and 2 of "Implications for future practice"

28-L270-271: If you mention shared decision-making, discussing a review of that literature would fit in this paper.

Reply 28: A full review of the literature in this topic would be beyond the scope of this review focused more on WWLST in this population and its implications on morbidity and mortality, so we have summarized the suggestions for shared decision making from the guidelines but not any of the published studies in this area. We have also included this as a suggestion for future research.

Changes in the text: "Due to difficulty in prognostication, each of the above guidelines emphasises the need for shared decision making with parents and for open communication. The practical advice for this is consistent and is summarised below:65, 66, 68-73

•Open and timely communication should occur with clear documentation of all discussions and their nature during the end of life process

•Parents should be provided with clear, unbiased information as to the prognosis of their child, the reasons, benefits and consequences of both continuing LST and WWLST. Uncertainty in prognosis should be recognised.

•Decision making should take part with the multidisciplinary team and those involved should identify themselves and their roles clearly.

•A care plan should be agreed to and revisited with changing information or prognosis

• Shared decision making can reduce the parental burden and stress of making complex medical decisions about their child alone.

•It is appropriate to encourage the sourcing of a second opinion where either party is unsure.

Several studies have been performed on shared decision making in end-of-life care within paediatrics and the NICU specifically. No systematic review currently exists in this area and would be interesting to further verify the above advice in future research."

29-L291-292: Why concentrate on just periviable infants as long as they are included in the study population? We initiate WWLST for older ELBW infants as well. That influences their morbidity and mortality rates.

Reply 29: We were hoping not to confound the two in this particular literature review but future research could also be aimed at this group as another factor which might cause a baby to be on the "edge of viability." Currently most guidelines or commentary regarding the "viability" of an infant are related to Gestational Age

but we recognize this is not the only factor involved in this condition.
Changes in the text: We have added the following sentence "One could also consider whether a "periviable" population should be expanded to include extremely low birthweight infants regardless of gestation as this is another significant indicator of survival.10"

30-L295-296: I do not understand this sentence. Please clarify.
Reply 30: Note, we have attempted to be more clear
Changes in the text: "The existing international datasets relating to premature birth are relatively heterogenous, without clear definitions or protocols for standardisation between them.78"

31-L302-312: I recommend reworking this paragraph including the advantages as well as disadvantages of large network studies. Also, I suggest including advantages and disadvantages of single center studies, while you are on the topic. The meaning of the last sentence is unclear, please clarify (and maybe include the neonatal reserach network in the US). Or exclude this paragraph.
Reply 31: We have considered this observation and incorporated this into the paragraph
Changes in the text: Please see the last paragraph in "Evaluating the literature"

32-L314-319: I think this paragraph belongs with the previous paragraph. Is iNeo similar to the NRN in the US? It still has problems of publishing data often 5 years out of date.
Reply 32: We have re-worked this paragraph
Changes in the text: Please see the last paragraph in "Evaluating the literature"

33-L346: I recommend taking out the term "significantly" since it does not refer to statistics.
Reply 33: Noted
Changes in the text: "significantly" removed

34-L350-351: What is a "clearer agenda?" So many factors play into inter-center variability, that more studies to evaluate inter-center reliability may be important. And since (as was documented in this manuscript, culture, religion, law, and unit culture and policy affect WWLST rates, I'm thinking a clear agenda may be counterproductive. Also, how does a clear agenda differ from guidelines?
Reply 34: This is a good point, we have re-worded the remaining paragraph to hopefully be clearer
Changes in the text: "While strict practice guidelines based on gestational age thresholds may not be necessary, nor appropriate in end of life decision making, guidelines for working though the decision making process behind WWLST could hopefully see a decrease in inter-centre variability, or at the very least, minimise lack of education as a barrier to engaging in WWLST discussions."

35-L354-355: As mentioned above, I'm not clear how concentrating on periviable

babies only would help clarify the picture.
Reply 35: Part of the reasoning for focusing on this population is that it has the larges differences and most recent changes in survival with the added benefit of improved technology. We have tried to address why periviable infants in the rationale and throughout the rest of the review more clearly.
Changes in the text: multiple areas in the text, re-worded conclusion

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Reviewer B

This manuscript, titled "Withdrawal and Withholding of Life Sustaining Treatment in Periviable Infants: Exploring Factors Affecting Outcomes - A Narrative Review" comprehensively explores a critical and under-researched aspect of neonatal care. The following review points out the need for improvement in various areas to enhance the manuscript's clarity, transparency, and overall impact. Here is a summary of the key points:
Title: The title of the manuscript is relatively long, and while it effectively conveys the focus and question of the narrative review, it is important to balance informativeness with avoiding excessive length. Readers generally appreciate concise and clear titles. Additionally, there is no running title mentioned on the title page.
Abstract: In the abstract, it is advisable to expand the abbreviation "WWLST" when used for the first time. While abbreviations should generally be avoided in abstracts, expanding them upon first use enhances clarity.

Introduction:

• There is no need to use the abbreviations "CPR" and "ACS," which are not used elsewhere in the manuscript.

Reply 1: Thank you for drawing our attention to this
Changes in the text: abbreviations expanded

• Definitions for withdrawal and withholding of care are lacking, and it is recommended to include clear explanations differentiating between withholding and withdrawal.

Reply 2: We have reviewed the literature and found a clearer definition of each
Changes in the text: “WWLST relates to the decision to limit the escalation of (withholding) or cease (withdrawal) life sustaining practices in the neonatal intensive care unit (NICU). In most cases, “life sustaining treatment” refers to mechanical ventilation. It may also include, but is not limited to, ionotropic support, cardiopulmonary resuscitation, nutrition and hydration. WWLST is most often considered in infants with severe complications where death is not imminent, but neonatologists predict mortality or poor outcomes will arise.24-26”

• Although the manuscript is a narrative review, it presents a hypothesis that could be better aligned with the narrative review approach by rephrasing it as a research question or objective. It's important to clarify that the goal of a narrative review is

to synthesize existing literature, not to prove or disprove a hypothesis.
Reply 3: We have changed this sentence.
Changes in the text: "Thus, we must investigate whether WWLST might be a crucial source of outcome variation in periviable infants."

• The incorrect mention of Table 2 instead of Table 3 should be corrected, and the interpretation of Table 3 could be summarized in sentences for easier reader understanding.
Reply 4: Thank you for drawing our attention to this, we have re-numbered the tables correctly
Changes in the text: Table numbers corrected, description of the table included with Table 1 (previously Table 3)

• While the percentage of survival has been addressed, neurodevelopmental outcomes have not been discussed. It would be beneficial to provide a summary interpretation of Table 3, offering insights into the rates of survival for different gestational ages.
Reply 5: Summary provided with Table 1 (previously Table 3), rates of neurodevelopmental impairment have been referenced in the review but there was not room or scope to include a full assessment of current rates in the literature
Changes in the text: "Neurodevelopmental impairment is an outcome of significant interest in previable infants. It has been noted that survival without neurodevelopmental impairment has improved over time, however the proportion of those infants who survive with ongoing neurodevelopmental deficits has remained the same.3, 20"

Methods:
• While the methods section is detailed, the manuscript lacks a strict search protocol, impacting the reproducibility of the study. It would benefit from more clarity on the criteria used for article selection.
Reply 6: The manuscript is a narrative review and thus does not need the same rigorous search strategy required for a systematic review. We have attempted to make out methodology as transparent as possible given this, recognizing (in the strengths and limitations section) the potential biases this might bring
Changes in the text: Improved clarity in the methods section

• The Methods section could benefit from more details on the rationale for the time frame and the criteria used to select studies, enhancing transparency and reproducibility.
Reply 7: The timeframe rationale has now been included
Changes in the text: "Studies up to fifteen years old were consulted to balance the need for data reflecting recency of practice and finding an adequate range of studies in what has previously been a sparsely published topic."

• Consider mentioning the use of PRISMA guidelines for the search and reporting process. Additionally, it is recommended that the Author incorporate a PRISMA

flow chart to provide a concise summary of the reviewed, excluded, and ultimately included articles in the final review.
Reply 8: PRISMA guidelines unfortunately do not relate to narrative reviews – they are for systematic reviews and meta-analyses
Changes in the text: James et al has also now been cited in this sentence.

• Expand the abbreviation "EPT" for clarity.
Reply 9: we have expanded this
Changes in the text: "extremely preterm infants"

• Clarify what is inferred by "infants of younger gestations," specifying a gestational age cutoff.
Reply 10: Thank you we have amended this
Changes in the text: "Very few studies look at the periviable period specifically but studies on general NICU populations found higher rates of WWLST in lower gestations, especially those infants 22-23 weeks' gestational age.26, 35"

Content
• The subheading used as "main body" does not adhere to the journal's guidelines for authors, which explicitly state that the term "main body" should not be utilized as a subheading. Authors are encouraged to choose appropriate subheadings for the content within this section.
Reply 11: We have changed the heading
Changes in the text: "3. Literature Review"

• Consider shortening the subheading "Withdrawal and Withholding of Life-Sustaining Treatment in the Neonatal Intensive Care Unit" to something more concise, such as "WWLST in NICU."
Reply 12: Thank you for drawing our attention to this
Changes in the text: James et al has also now been cited in this sentence.

• The contradiction between the statement (line 251) about focusing on literature and guidelines from the last 15 years and the search strategy of 2 years needs to be addressed.
Reply 13: The search was conducted over two years but the studies included were from up to 15 years ago. We have tried to make this clearer in the revised methods section.
Changes in the text: "Multiple searches were conducted over a period from March 2021 to June 2023 delving into different aspects of the topic, allowing for a wide base of literature from which to draw." and "Studies up to fifteen years old were consulted to balance the need for data reflecting recency of practice and finding an adequate range of studies in what has previously been a sparsely published topic"

• Expand the abbreviation "BAPM" on line 261.
Reply 14: We have expanded this abbreviation

Changes in the text: “British Association of Perinatal Medicine”

• The term "No Escalation of Treatment -strategy" is not mentioned throughout the manuscript.

Reply 15: Thank you for drawing this to our attention. This may be a decision arrived at in cases where WWLST discussions results in an intermediate state, whereby NICU care continues but no escalation of treatment level to include CPR will occur. This may be a temporary step while more discussions take place or sometimes is an end result of the discussions.

Changes in the text: We have expanded the sentence in lines 243 and 244.

• The subheading 'Outcomes after WWLST' requires a more detailed discussion to align with the manuscript's title and purpose. Further elaboration on the spectrum of outcomes for infants born in the periviable period after WWLST is essential.

Reply 16: This is a valid point and the section has been expanded to include this.

Changes in the text: See the paragraph “Outcomes after WWLST”

• Provide more clarity on the limitations of the review, discussing potential sources of bias and addressing the possibility of publication bias, especially when dealing with studies from different countries and regions.

Reply 17: Thank you for this suggestion. We have expanded this section in line with above.

Changes in the text: See “Strengths and Limitations of this Review” there are also comments regarding the generalizability across other nations in the “Variations in Practice” section

It is advisable to enhance the comprehensiveness of the review by incorporating several noteworthy articles pertinent to the topic of withholding and withdrawal of care. Below, I have listed a few significant articles that were not included in the current review.

• Boutillier B, Biran V, Janvier A, Barrington KJ. Survival and Long-Term Outcomes of Children Who Survived after End-of-Life Decisions in a Neonatal Intensive Care Unit. J Pediatr. 2023;259:113422. doi:10.1016/j.jpeds.2023.113422

• Yotani, N., Nabetani, M., Feudtner, C., Honda, J., Kizawa, Y., & Iijima, K. (2020). Withholding and withdrawal of life-sustaining treatments for neonate in Japan: Are hospital practices associated with physicians’ beliefs, practices, or perceived barriers? Early Human Development, 141, 104931. https://doi.org/10.1016/j.earlhumdev.2019.104931.

• Harris, L. L., & Douma, C. (2010). End-of-life Care in the NICU: A Family-centered Approach. NeoReviews, 11(4), e194–e199. https://doi.org/10.1542/neo.11-4-e194.

• Kornhauser Cerar L, Lucovnik M. Ethical Dilemmas in Neonatal Care at the Limit of Viability. Children. 2023; 10(5):784. https://doi.org/10.3390/children10050784.

• Kim, S., Savage, T. A., Hershberger, P. E., & Kavanaugh, K. (2019). End-of-Life Care

in Neonatal Intensive Care Units from an Asian Perspective: An Integrative Review of the Research Literature. Journal of Palliative Medicine, 22(7), 848–857.

• Gkiougki E, Chatziioannidis I, Pouliakis A, Iacovidou N. Periviable birth: A review of ethical considerations. Hippokratia. 2021;25(1):1-7.

Reply 18: These articles have been very helpful and we appreciate your highlighting these.

Changes in the text: The studies have been read and incorporated into the review where appropriate

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In conclusion, while the manuscript "Withdrawal and Withholding of Life Sustaining Treatment in Periviable Infants: Exploring Factors Affecting Outcomes - A Narrative Review" addresses a crucial and under-researched aspect of neonatal care, there are opportunities for improvement to enhance clarity, adherence to guidelines, and overall impact. The suggested revisions, primarily focusing on minor adjustments in the title, abstract, introduction, methods, and content presentation, aim to refine the manuscript and ensure its alignment with journal guidelines. With these suggested changes, the manuscript has the potential to make a significant contribution to the literature on periviable infants' care, making it recommendable for acceptance after minor revision.

Reviewer C

Abstract:

"Further, the variation patterns are similar to those of overall outcomes - increased variation in decreasing gestational age". This statement needs to be rephrased as it is not clear.

Reply 1: We have attempted to rephrase this sentence for clarity.

Changes in the text: "Variation increases as gestational age decreases."

Introduction:

- "The magnitude of difference in survival rates between units has been likened to the improvement in survival attributed to antenatal corticosteroids (ACS), surfactant or an extra week of gestational age". Please rephrase this statement as it is not clear. Consider using attributed to or similar terms.

Reply 2: The difference was not attributed to antenatal corticosteroids or an extra week of life, it has the same magnitude as the effect these factors have. We have tried to clarify this in the revised sentence.

Changes in the text: "This difference in survival between units has been likened to the magnitude of improvement in survival attributed to antenatal corticosteroids, use of surfactant 17, 20 or an extra week of gestational age.21"

- "Table 2 highlights key studies over the last fifteen years which reported survival statistics in
periviable infants in high income countries". This should be Table 3 and not 2. Also please arrange studies in Table 3 in chronological order, may consider adding

reason for death in periviable neonates to the table. Consider renumbering your tables.

Reply 3: Thank you for noting this, we have amended the table numbering.
Changes in the text: Table numbering corrected

- Importantly, despite a gross consensus regarding gestational age limits, there was often a spectrum of responses between neonatologists of the (within) same country. Consider using variation instead.

Reply 4: We have changed the wording of this
Changes in the text: "Surveys of neonatal clinicians have found individual neonatologists' thresholds for resuscitation at periviability vary between and even within countries."

- Paragraph from line 84 to 94 seems to be redundant and not flowing. It needs to be rewritten as it is not clear and does not deliver a meaning.

Reply 5: agreed
Changes in the text: This section has been largely deleted and some of it reworked into other paragraphs.

- The background and rationale is not well written and redundant with no clear statement of why this review was conducted.

Reply 6: We have reworked the background and rationale to be clearer
Changes in the text: See "Background and Rationale"

Methods:
- The authors did not explain why they chose this time frame for their search which is important to highlight (? Increase resuscitation at limit of viability, etc…..)

Reply 7: We have now included the rationale for this timeframe
Changes in the text: "Studies up to fifteen years old were consulted to balance the need for data reflecting recency of practice and finding an adequate range of studies in what has previously been a sparsely published topic."

- The search and this review was aimed at studies describing developed countries and their practices – this statement is not clear, needs to be rewritten.

Reply 8: Thank you for this feedback we have changed this.
Changes in the text: "This review includes studies in English describing end of life practices in developed countries only as the characteristics of a periviable population in a low-resource setting might not be comparable."

- "EPT infants": This term was used for the first time in the methods section without referral to what it stands for.

Reply 9: Noted
Changes in the text: "extremely preterm infants"

- Line 126-138 is poorly written and largely speculative.

Reply 10: This section has evidence supporting the claims with commentary tyring

to suggest reasons for the data. We have attempted to remove the speculative language.
Changes in the text: "Some studies suggest that neonatologists are increasingly deciding to institute WWLST.28, 36 This may be a better recognition of medical futility,28 or potentially because neonatologists are increasingly routinely resuscitating infants of lower gestational ages at birth who are at greater risk of subsequent deterioration. In most cases, withdrawal is by cessation of respiratory support.26, 32 WWLST is commonly used to provide a peaceful and controlled death to avoid suffering, pain or expected poor long-term outcomes.29"

- Line 144-147: these are not prognostic factors but clinical indicators.
Reply 11: Noted
Changes in the text: "Factors that have been associated with discussions about WWLST include being male, white ethnicity, <24 weeks gestation, small for gestational age, congenital malformations/syndromes, early-onset sepsis, severe brain injury and necrotising enterocolitis,25, 26 which would reflect commonly recognised neonatal clinical indicators"

- Line 148-149: not sure where authors drove this conclusion from. The authors need to elaborate on why this is true if they believe so.
Reply 12: The studies in which this claim came from are cited in the text
Changes in the text: These studies are cited in the text after the sentence referred to above

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- The manuscript body is poorly written with a lot of grammatical errors and unclear content. This made it very hard to understand its content as well as its intent.
- Could not finish reviewing it all due to large burden of grammatical errors as well as largely speculative statements and inaccurate content.
Reply 13: Thank you reviewing what you were able to. We have made an effort to ensure the grammatical errors have been identified and corrected.

Reviewer D

Your study is about a very interesting topic and gaining knowledge about the influence of WWLST on extremely preterm neonates' mortality is valuable and I congratulate you for investigating this topic.
With very few publications on the subject, I wonder if a more systematic methodology could be able to identify other references. You did not comment on what didn't you allow you to perform a systematic review.
Reply 1: Thank you, we agree more systematic methodology may be useful. We found that individual searches with relevant search terms were often returning very little or several unrelated studies. With few studies on the topic we were more aiming to characterize and understand the literature which exists on this topic in order to inform future research including systematic reviews rather than to perform one ourselves.

Changes in the text: "Multiple searches were conducted over a period from March 2021 to June 2023 delving into different aspects of the topic, allowing for a wide base of literature from which to draw. Other articles were sourced from scoping searches and from the references of included papers."

You looked at WWLST reporting in periviable gestational ages. How is reporting of WWLST in higher GA ? Are neonatologists less inclined to communicate about their practices in these periviable situations ?
Reply 2: This is an interesting question and one not directly addressed by this review as it was outside the scope.
Changes in the text: none

You mention cultural differences between countries and within countries. Are you able to describe them more like it was done in previous adult ICU papers within Europe ? (Sprung JAMA 2019)
Reply 3: We have attempted to highlight cultural differences further by re-visiting the literature
Changes in the text: See "Variations in Practice"

With the data at your disposal, are you able to tell if the centers resuscitating more EPT neonates are doing more or less WWLST?
Reply 4: This is an interesting take and one that was difficult to verify. Studies usually either focused on active management or WWLST but not both.
Changes in the text: We have included it as a suggestion for future research.

What is your opinion regarding specific guidelines for WWLST for periviable infants ? Are there any specificities for this population or shouldn't the process be similar whatever the patient's age when the prognosis is poor ?
Reply 5: We have tried to expand on our opinion of guidelines. Essentially these authors are for the use of guidelines to aid in formalizing processes around WWLST but given the case-by-case nature of periviable infant management we have suggested that strict gestational age cutoffs are likely unhelpful.
Changes in the text: "Ultimately, the intention of guidelines for WWLST of periviable infants should focus on the process and execution of WWLST in periviable infants, rather than creating a set of rigid clinical criteria on which to determine a periviable infant's likely course of treatment."

Below are more specific comments about your text and tables, that require some adjustments:
Line 73. Table 3, not table 2, gives a summary of very preterm infants' survival
Reply 6: Thank you we have corrected the inaccurate numbering.
Changes in the text: Tables corrected

Table 3: Adding the number of patients and not only the proportion would give a better insight in these former reports.
Reply 7: Within the timeframe for responding to the reviews, we did not have the

time to add the number of patients to the table and respectfully ask if we could have the table as submitted.
Changes in the text: -

Table 4 is not mentioned in the text.
Reply 8: We have corrected this
Changes in the text: Table 4 now referred to in the text

Line 132: lower gestational ages.
Reply 9: We have amended this
Changes in the text: "lower gestational ages"

Line 145 : SGA abbreviation.
Reply 10: we have expanded this
Changes in the text: "small for gestational age"

Line 147 : Incomplete sentence.
Reply 11: We have corrected this
Changes in the text: "Factors that have been associated with discussions about WWLST include being male, white ethnicity, <24 weeks gestation, small for gestational age, congenital malformations/syndromes, early-onset sepsis, severe brain injury and necrotising enterocolitis,25, 26 which would reflect commonly recognised neonatal clinical indicators"

Line 148-149 : Do we know if discussion about WWLST is less likely to happen for these populations as well ? Punctation is missing.
Reply 12: yes and this has now been included
Changes in the text: "Life sustaining treatment is also more likely to be withheld or withdrawn in white infants than in Black or Hispanic infants 25, 26, 32 and families of white infants are more likely to be approached for discussions about WWLST.25"

Line 149: Who gives these main reasons ? Physicians, family, both ?
Reply 13: We have clarified where these reasons were from
Changes in the text: "Reasons for continuing LST after it's limitation or withdrawal recorded in the medical record were multifactorial, including non-acceptance of prognosis/diagnosis, religion, culture, personal and in some cases the reason was unknown.33"

Line 156: Do we know how often parents raise the discussion before physicians do ?
Reply 14: It is not often cited but one study (Hellmann et al. suggests 83% of cases)
Changes in the text: "Clinicians usually raise the discussion about WWLST (83% of the time in 19 tertiary units in Canada),29 but parents are very involved the subsequent decisions, between 86.5% and 98% of the time.28, 31, 34, 39"

Line 159: Please clarifiy what you mean by “involved”
Reply 15: as below
Changes in the text: “However, when an infant died on full intensive care measures and received CPR, as few as 47% of parents were involved in end of life decision making.28”

Line 163: either “in many cases” or “usually” but not both.
Reply 16: We have amended this
Changes in the text: deleted “in many cases”

Line 165: Unfortunate formulation. Parents do not withdraw care !
Reply 17: Thank you for drawing our attention to this! We have rephrased.
Changes in the text: “However, up to three-quarters of parents eventually withdraw or limit LST after discussions about WWLST.25, 33”

Line 172: How much is a small proportion ? According to Line 165, it could be a quarter. I find “despite WWLST” judgmental.
Reply 18: We have amended the text to address the above
Changes in the text: “About one-quarter (22-24%) of parents decide to continue life sustaining care following WWLST discussions.25, 33”

Line 182: Unfortunate formulate: WWLST is not withholding or withdrawing care but life-sustaining measures. This has a very different meaning for families and HCW.
Reply 19: Thank you we have amended this
Changes in the text: We have amended this in various sections of the text

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Line 195: Do these papers give number of WWLST and survival to give an idea about this relation (more WWLST = less survival in EPT ?)
Reply 20: This has not beed specifically addressed in the current papers, there are no direct comparisons between rates of WWLST and survival currently.
Changes in the text: none

Line 197-203: Unclear. Please review this paragraph.
Reply 21: We have attempted to clarify the intention of the paragraph
Changes in the text: See paragraph 2 of “Variations in Practice”

Line 207: “Such” haemorrhages, what do you refer to ?
Reply 22: Intracranial haemorrhages
Changes in the text: “However, as Chevalier et al. points out, the outcomes due to intracranial haemorrhage are often uncertain and different depending on site, laterality and subsequent neurological symptoms.”

Line 209: “Papile grading”: please clarify for non-expert readers.
Reply 23: We have included a definition
Changes in the text: “Papile grading (a radiological grading system denoting the

severity of intracranial haemorrhage from I (mild) to IV (severe))46"

Line 212-213: can you justify this affirmation with evidence ?
Reply 24: We have re-worded this sentence/affirmation to be in line with the literature
Changes in the text: "Dworetz et al. suggests that several factors might be involved in the variation between units with regards to WWLST including institutional policy, geographic region, personal differences in race/ethnicity, culture, religion or spirituality and medical differences related to the population characteristics of that specific cohort of infants.26"

Line 227: what kind of threshold ? GA, brain injury, other ?
Reply 25: The threshold is for survival estimates
Changes in the text: "Interestingly, the estimated chance of survival as a threshold for when neonatologists will intervene over parental wishes ranges widely.58"

Line 260: broader ?
Reply 26: Amended
Changes in the text: "broader"

Line 298: Table 3?
Reply 27: We have corrected table numbering
Changes in the text: Table numbers now correct

Line 300: Complete the sentence: It was much lower when expressed with all live births instead of what ?
Reply 28: We have completed the sentence
Changes in the text: "This was well illustrated by Myrhaug et al. where all the estimates of survival were much lower when expressed as a percentage of all live births as compared with NICU admissions.4"

Line 326: reproductible.
Reply 29: We believe the spelling in the text is correct as per the Oxford Dictionary
Changes in the text: "reproducible"

Line 336: what do you mean by that ? Please rephrase.
Reply 30: We have reviewed and rephrased
Changes in the text: "Up to date outcome statistics from recent years are lacking across the board. While this data may exist in annual reports from neonatal networks, it is yet to make it to published studies. This delay means that most published research studies on extremely preterm/periviable infants relate to cohorts five to ten years old at best. Additionally, many studies from the last 15 years re-analyse a limited data pool from existing large population based studies such as EPICURE79 and EPIPAGE-280 which supports the need for more comparative and up to date survival data.81"