APPENDIX 1 Summary of comments from the ISSFAL membership and Board for the ISSFAL Statement – Omega-3 fatty acids during pregnancy and preterm birth.

The table summarizes comments received, groups them into themes and details how the draft Statement has been modified to address these comments.

Theme of Comments	Comment/s Received	Modification to Statement and Rationale
This statement in relation to other Recommendations	Include omega-3 recommendations for pregnant women from other expert scientific bodies in this statement.	- Reference to previously published recommendations has been included in the Introduction. This gives context to the body evidence available at the time of publishing past recommendations compared to the synthesis of contemporary evidence and revised recommendations for omega-3 in pregnancy, specifically in relation to prevent preterm birth.
Baseline status and efficacy of supplementation	Request to reduce emphasis on suggestion of harm from ORIP secondary analysis as not seen in other trials and may distort perceptions of benefit.	- ORIP is the largest trial, and it is not possible to completely ignore its results.[1] ORIP had about 2770 women per group[1] compared with 1700 per group in Olsen 2019[2], 1200 per group in DOMInO[3] and about 500 per group in ADORE.[4] - Instead, the ORIP secondary analysis[5] is considered together with other equivalent analyses from ADORE[4] and the Harper[6] trials, suggesting careful consideration to achieve maximum benefit of supplementation while minimizing risk and unnecessary treatment.
	Disagreement that women with replete status will not benefit from supplementation.	- It is not clear from the available data to indicate whether women with replete status will or will not benefit from supplementation to reduce risk of prematurity. - The statement highlights that correction of status for women at lower end of the distribution who will benefit most from omega-3 supplementation in pregnancy.
Determining and defining low omega-3 status	Request for clear definitions around what is considered low omega-3 status and a cut-off or some value below which low in blood omega-3 status is defined.	- Clarity around cut-offs where supplementation provides clear benefit to reducing the risk of early birth are included for higher income settings. - It is also noted that there are currently no clearly agreed definitions internationally and work is required to confirm the clinical validity of the cut-offs derived from the largest trial to date.
	Vegan/Vegetarian women.	- Further information has been included about omega-3 status for vegan/vegetarian women and potential supplementation sources. Commentary is also made about lower income settings and the

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		potential issues of extrapolating prematurity risk in such settings because of low intakes/vegetarianism.
	Equity of access to omega-3 testing.	- Recommendations have been expanded to consider alternatives in the absence of available omega-3 testing. The limitations of alternative methods of assessing omega-3 status are discussed and measurement of blood is proposed as the gold standard as per current ISSFAL Official Statement Number 6.[7]
	Clarification around standardization and consistency of measurement between localities.	- Discussion around omega-3 blood fractions and reference to formalized measurements and high comparability between labs has been added.
	Clarification around best biomarker to use to measure omega-3 status.	- We report current evidence on biomarkers for measurement and suggest future investigation to further assess different measures of omega-3 status for decision-making around omega-3 supplementation to reduce risk of early birth.
Omega-3 Supplementation	Specifying the dose in mg EPA+DHA per kg of body mass per day.	- Not included as dose per kg unlikely to be appropriate approach especially in pregnancy.
	Ratio EPA to DHA in supplements.	- Highlighted likely mechanisms of EPA and DHA. Emphasized that a combination of DHA and EPA are effective as evidenced in the subgroup analysis of the 2018 Cochrane.[1]
	Timing of supplementation.	- Timing of supplementation addressed with supporting evidence from the 2018 Cochrane Review (from less than 20 weeks to 37 weeks/delivery).[1]
	Recommend supplementation based on EPA levels instead of DHA levels.	- Not included as current available evidence does not support this – as per evidence synthesis detailed in the Statement.
	Include other benefits of omega-3 supplementation.	- Other suggested protective effects of omega-3 supplementation in pregnancy (asthma/wheeze, sleep, neurodevelopment) have not been included to preserve the focus of the ISSFAL Statement on Preterm Birth.
	Quality of supplements.	- Addition of consideration for regulation of supplement manufacturing to ensure pregnant women can obtain high quality supplements that meet heavy metals, pesticides, and oxidation levels within accepted safe international standards.

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General clarification	Clarification around supplementation in the Adore Trial	- Emphasized that no EPA was provided in the trial.
	Clarification around ORIP Compliance and suggestion that poor compliance in ORIP may have overly influenced lack of omega-3 LCPUFA efficacy on prematurity reductions.	- The per-protocol (compliance) analysis of ORIP was reported in the original paper and the results did not differ from the intention to treat analysis.[1] We have also added a sentence in the statement. - Compliance analyses are not generally featured in the ISSFAL statement as only intention to treat analyses have been reported for most trials and these analyses are the most relevant for assessing the value and effectiveness of a general program or advice for omega-3 supplementation.
	Confusion between issues of bleeding with omega-3 LCPUFA supplementation and the special consideration that may be needed for women with coagulation disorders who require treatment with heparin.	- Specific advice regarding heparin has been removed as this issue would require medical consideration. Broad recommendation that omega-3 supplementation should be guided by a health professional has been included. - Statement that there is no increased bleeding risk for omega-3 LCPUFA supplementation in normal pregnancy included from the results of the Cochrane review.[8]
	Implementable recommendations for all countries irrespective of omega-3 testing availability.	- Recommendations revised to include broad advice, in relevant regions, as follows. ▪ Encourage adequate intakes of omega-3 LCPUFA for all women of childbearing age in line with existing dietary guidelines, with special attention given to the increased omega-3 LCPUFA requirements for pregnant women. ▪ Screen for omega-3 LCPUFA deficits in early pregnancy as is common for other nutrients vital for pregnancy health (such as iron, vitamin D). ▪ Address nutritional deficits in omega-3 LCPUFA by advising supplementation with a total of about 1g of EPA+DHA, taken daily from before 20 weeks' gestation.
Cochrane Review	Clarification around different versions of the Cochrane review.	- We have clearly defined the different versions of the Cochrane review end labelled the most recent update as the '2021 Cochrane Update' throughout the Statement for clarity. - Additional Section "Consistency with other systematic Reviews'.

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	Clarification prolonged gestation as an outcome.	- Prolonged gestation has been added as an outcome to Table 1, so it is clear how many trials included this outcome in the 2018[8] and the 2021 Cochrane Reviews. An explanation around this outcome and changes to obstetric practice has been included in the text for clarity.
	Explanation for reduction in % of PTB between Cochrane reviews.	- A section on consistency between systematic reviews has been added and reference to changes in results most likely due to heterogeneity between RCTs. We have also included further analysis of subgroups to address heterogeneity
	Request to state the results more explicitly.	- % and RR added to text.
	Request to state effective dose range.	- Dose range added to text.
	Request to analyze 2018 and 2021 Cochrane comparison by dose.	- Subgroup analyses for studies intervening with <500mg omega-3 LCPUFA, 500 to 1000 mg omega-3 LCPUFA or >1000 mg omega-3 LCPUFA in the 2021 Cochrane Update is included.

References

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