***WHO ERC***
**Review Summary**

**Protocol ID**: ERC.0004223
**Country:** Multi-country study (Bangladesh, Ethiopia, Kenya, Nigeria and Pakistan)
**Protocol Title:** Efficacy of probiotic supplementation in preterm and small for gestational age infants. A multi-centre, placebo- controlled, individually-randomised trial
**Version:** 1.1 **Dated:** 27/12/2024
**WHO Responsible Staff Member**: Karen Edmond
**Responsible Unit**: WHO/HQ/FWC/MCA
**Meeting Date**: 23/01/2025

Dear Dr. Karen Edmond,
Please find the review summary of the Protocol "Efficacy of probiotic supplementation in preterm and small for gestational age infants. A multi-centre, placebo- controlled, individually-randomised trial", which was submitted to the Secretariat on 17/12/2024. This proposal underwent regular review.

The outcome of the review is provided below. When responding, please submit the following:

1. A cover memorandum that addresses your responses, POINT BY POINT, to each of the queries in sections A and B.
   *Section C contains Suggestions to improve the proposal but there is no obligation to follow them.*

2. An Amended protocol including the responses in bold, highlighted or in track changes. Please ensure that tracking formatting changes is switched off or that all formatting changes have been accepted and that no comments which the team may exchange during the editing are included in the track changes version. The protocol should include all relevant documentation (ICF, study instruments, peer review, etc.) even if already submitted.

Please note that comments in the introductory paragraph are meant for the WHO Responsible Staff Member, though you may decide to share them with the PI.

PLEASE RESPOND TO THIS REVIEW SUMMARY WITHIN A 3 MONTH PERIOD, OR PROVIDE THE ERC SECRETARIAT A VALID JUSTIFICATION FOR THE DELAY.

The ERC considered this a clear and well written study protocol. There are some specific points to be addressed in the protocol and site specific information to be provided as to understand how the study will be applied in the different countries. Please see specific comments below.

The ERC would like to thank the study team for having included the researchers' statements in the certificate of consent. This was highly appreciated as it reflects a clear understanding of researchers responsibilities with regards to participants understanding during the consent process.

## A. Amendments (Response and change required)

*This section includes queries and comments on your protocol, study instruments or the informed consent form for which the ERC requires your response and where relevant, appropriate amendments to the protocol, study instruments or the informed consent.*

1. Protocol

1.1. Please provide an amended proposal specifying the version number and/or date on each page.

**In relation to potential risks and benefits:**

1.2. Supplements will be delivered by the study near the hospital wards or in the individual homes of participating infants. Infants will have regular in person visits from the study team; daily for 28 days for supplement administration and subsequent visits for follow up outcome assessment.

1.2.1. Please describe what will be done in case researchers identify problems placing the baby and/or mother at serious risk of harm.

1.2.2. There may be some issues that require mandatory reporting and they should be addressed in the protocol and the consent documents. Mothers should be alerted to the fact that there could be situations where confidentiality has to be broken. In addition, the procedures that researchers should follow in such cases are to be specified.

**In relation to fairness:**

1.3. The study proposes to only include adult women. Given the subject under study and the fact that babies of adolescent mothers face higher risks of low birth weight, preterm birth and severe neonatal conditions, it would be relevant to include minors. They may represent an important sub-population in some countries and may highly benefit from the study activities (i.e. visits, follow up, etc). In several countries minors who give birth are considered emancipated minors which allows them to access research without parental consent. Because pregnant minors and babies born to a minor are at higher risks, the ERC considers that they should be allowed to access research in general and this study in particular as much as possible. Please discuss.

1.4. Please state the composition and describe the roles and responsibilities of the Data Safety Monitoring Board (DSMB).

1.5. Please explain the plans to facilitate access to probiotics at the different sites should the intervention prove to be beneficial to newborns. It is also important to provide information on the engagement of the Ministries of Health in this regard.

1.6. Information on ethnicity will be collected. Please explain how such information will be analysed in the context of the study and how such data will inform the study objectives.

**With regards to the consent process, confidentiality and privacy**

1.7. Section 7.1 states that women's permission will be requested to be approached by the research screening team. Please specify when hospital staff will ask mothers' authorization for this purpose.

1.8. While sections 22.3 and 23 indicate that all mothers will be given time to reflect on participation, this information is not reflected in other pertinent sections (e.g. 22.2, 7.1, etc.). Please specify the time that will be given to mothers to reflect their possible participation in the study and the specific process involved in then obtaining consent.

1.9. Section 17.4 states "This trial will generate an anonymized research dataset". However, it is stated that "trial data for each participant will be identified by a unique anonymous ID number. The words "anonymization" and "de-identification" seem to be used interchangeably. If IDs are used, the participant personal information is linked to the participant data through the ID. As a consequence, the data is not anonymous but coded. It would be anonymous if at some point, the key that links the personal data with the participant was destroyed. Please clarify whether this will be the case and make necessary changes across the protocol. In addition, please clarify the type of data (i.e. anonymous, coded, etc.) that WHO will receive (section 17.5).

1.10. Section 17.4 states that after completion of the trial, documents will be archived in accordance with institutional and national rules for clinical research archiving. Please provide a standardized timeline to be applied across study sites. Such a timeline should be appropriate to ensure data access if needed (e.g. after publication) but reasonably short as to ensure that data are not being unnecessarily kept. It should be stated who will have access to data, where it will be safely stored, for how long data will be kept, and when it will be destroyed.

1.11. Annex 6 is intended to provide site specific characteristics. Some key components to understand how the study would be implemented at country level were stated in the annex. However, the content included in key components (e.g. community engagement, results dissemination, etc.) does not reflect country differences as the paragraphs read exactly the same for all countries. Please clearly state how exactly the study will be implemented in each country and include relevant information. Fundamental topics are listed below but please note that the list is not exhaustive:

1.11.1. The linkages that were established with the local institutions (government, health system, educational system, NGOs, associations, etc.) for different purposes (e.g. uptake of the intervention if proven beneficial, referrals, etc.
1.11.2. Where (i.e. health facility or household level) the different processes related to potential participation in the study will take place (i.e. permission from mothers to be contacted by the study team, consent for screening, consent for the trial, etc.)
1.11.3. Whether pregnant minors will be included.
1.11.4. The pathway that will be followed for referrals.
1.11.5. Where participant information will be safely stored, for how long and when it will be destroyed.
1.11.6. The tokens of appreciation that will be given to participants.
1.11.7. The community engagement process that will be followed
1.11.8. The dissemination plan that will be followed to inform participants of the results of the study as well as communities and stakeholders.

2. Study Instruments
2.1. Please provide the statistical analysis plan (section 18.1) once approved by RP2.

3. Informed Consent Forms
The contact details of the PI and the ethics review committee are provided in case participants have queries. Please also add the details of someone who is not in a position of authority, and that mothers feel more comfortable contacting. The person should be familiar with the study and able to answer questions.

**Screening Information Sheet:**

3.1. The information under "Right to refuse or withdraw" is confusing. If a mother has agreed to the study but then withdraws and the baby has not yet been screened, there will be no data. Therefore, the option to keep the data in the study would not be feasible. Please amend the wording.

**Main trial Information Sheet:**

3.2. Under "Purpose of the research" please increase objectivity in the phrase "So we will be able to show definitely what effects these probiotics have, if any, on rates of death, infections, bowel problems and growth in preterm and SGA infants". The words "…we will be able to show definitely…" may be replaced for example with "…we intend to show what effects these probiotics…" or similar.
3.3. Under "Probiotic supplements used in the trial" it is stated that a syringe will be offered to the mother to feed the baby. Please clarify that this will be a way to carefully put the liquid into the baby mouth and that no needle will be involved.

**B. Clarifications (Response required but change may not be required)**

*This section includes queries on your protocol, study instruments or the informed consent form for which the ERC requires to make changes to your protocol.*

1. Protocol
Section 5.2 states that study teams will be exactly the same for the different sites. Please clarify their composition in Annex 6.

**C. Suggestions**

*This section consists of suggestions for alternative scientific or technical approaches or methods for conducting the research but which do not raise critical, ethical issues. These are meant to be helpful to investigators and are presented as suggestions for you to consider incorporating into a revised protocol. No response from you is required for any comment in this section. If, however, you do make changes to the protocol as a result of these suggestions, please submit the revised protocol to the ERC.*

NIL

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Based on the above comments, the Committee has the following recommendation(s) for this proposal:

[ ] The proposal is ***Approved as submitted.*** No modifications are required.

[X] The proposal is ***Conditionally Approved; requires amendments and/or clarifications.*** Final approval is contingent upon an adequate response by the Principal Investigator, to the satisfaction of the reviewers or the Chair on behalf of the ERC.

[ ] The proposal is ***Not approved; requires additional information and/or rewriting.*** A revised version of the proposal should be re-submitted by the WHO responsible staff member as a new submission to the ERC for re-review by Committee.

[ ] The proposal is ***Rejected***. The proposal is ethically unacceptable, for the reasons stated above. The Principal Investigator may submit a new proposal that takes into consideration the ethical issues raised by the Committee. If you do not agree with the Committee's assessment, please feel free to submit an appeal to the Chair of the ERC, through the Secretariat.

**NOTE: Final Approval of the Proposal is contingent upon submission of the following:**

[ ] Local ethics approval(s) [ ] Other relevant documents

The ERC would like to receive a copy of the recommendations of the local ethics committee when available.

***IMPORTANT***

1. *Any changes to the proposal or to the attachments (informed consent/study instruments etc.) should be approved by ERC before being implemented.*
2. *The approval for this proposal is valid for a period of* ***one year only.***
3. *Please resubmit this proposal for a Continuing Review at least 2 months before the next re-approval period.*

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**Chairperson** Antonella Lavelanet **Date** 30 January 2025

**Name: Antonella Lavelanet**

**FINAL APPROVAL**

Amendments and Clarifications to the proposal have been reviewed. The protocol (Version: 1.3 Date: 30.03.2025) and informed consent Forms (Dated: 30.03.2025 ) submitted on 7.04.2025 are approved by the ERC

Please ensure the ERC-approved versions of the protocol and consent forms are shared with the local ethics committees. This approval extends to Nigeria. Final approval for the Bangladesh, Ethiopia, Kenya, and Pakistan site are pending receipt of local ethics approval.

**Chairperson** Ehsan Shamsi Gooshki

**Name** Ehsan.Shamsi.Gooshki

**Date** 16/04/2025

**FOR THE SECRETARIAT**

Amendments and Clarifications to be reviewed:
[ ] Electronically by ERC
[ ] by Primary reviewers
[ ] by Secretariat

Amendments approved / Clarifications accepted on
Local ERC approval(s) obtained on Nigeria: 7.03.2025
Relevant Documents submitted on 13.04.2025
Comments:

Signature Date 15.04.2025