WHO ERC
Review Summary

Protocol ID: ERC.0002901
Country: Master Protocol
Protocol Title: A multi-country randomized clinical trial to evaluate the impact of continuous KMC initiated immediately after birth compared to KMC initiated after stabilization in newborns with birth weight 1.0 to <1.8 kg. on their survival in low-resource settings.
Version: 1.0 **Dated:** 12/04/2017
WHO Responsible Staff Member: Rajiv Bahl
Responsible Unit: WHO/HQ/FCH/CAH
Meeting Date: 08/06/2017

Dear Dr. Rajiv Bahl,
Please find the review summary of the Protocol "A multi-country randomized clinical trial to evaluate the impact of continuous KMC initiated immediately after birth compared to KMC initiated after stabilization in newborns with birth weight 1.0 to <1.8 kg on their survival in low-resource settings.", which was submitted to the Secretariat on 13/04/2017. 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 an important study. The main ethical concerns related to the timing of the consent process among women that were not pre-consented during the antenatal period. The ERC considered that a woman who has just delivered a small baby will not be in condition to understand the study and to decide whether to take part as her autonomy will be diminished. Please find specific comments below.

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.
1.2. The aim of the study is clear, however, the protocol should provide background information on the KMC method for the non-specialists to understand how skin-to-skin contact will enhance survival and therefore, reduce mortality.
1.3. The protocol makes reference to formative research that will be conducted in each site. Please further describe how the preparatory phase will involve women and communities.

In relation to safety:

1.4. Annex 1 provides some site specific information on the facilities where the study will be conducted. However, the level of experience and implementation of KMC per facility is not stated. Given the variability of intra hospital mortality in the study population; from 16.3% in India to 48.2% in Nigeria, it would be important to describe the level of implementation and experience of personnel with KMC as well as the percentage of babies that have to be pulled out from KMC at the different sites.

1.5. Please state whether a specialist on breastfeeding will be available to support mothers in the difficult situation of feeding a very small baby (1.0 to <1.8kg) and, in some cases, after a difficult delivery (C-section).

1.6. The population under study has a high mortality rate. High quality data on the potential benefits and harms will be critical. Please provide a data and safety monitoring plan with a description and justification regarding how comprehensive and satisfactory monitoring will be assured (e.g. a full SOP on data and safety monitoring).

In relation to the consent process:

1.7. The study team proposes to pre-consent mothers at risk of having a baby with low birth as per the inclusion criteria. The ERC welcomes this alternative as women will be able to think, understand and reflect on the study prior to delivery. It was considered that the consent document to be used after delivery is extremely long and burdensome. Mothers will be tired and stressed after delivery and asking questions to ensure understanding would add to their difficult emotional situation. Please shorten the consent document to a minimum providing clear and concrete information that is directed to lay persons. This document should confirm consent rather than promote the consent process again.

1.8. In relation to the previous point, please specify who will consent potential participants and whether counselling will be available.

1.9. The ERC considers that the sub-set of women who have just given birth to low birth weight babies have vulnerabilities additional to those inherent to women in the immediate post-partum period. For those women who were not pre-consented, the ERC recommends that the research team(s) should consider developing criteria to guide the person obtaining consent to assess whether the women are in a mental and emotional state to understand the consent process, and understand that they are being asked to take part in a research study that involves their pre-term/LBW baby. Alternatively, and if possible, the study team could delay the initiation of the consent process/recruitment till, based on objective criteria, the mother is emotionally and physically stable to be able to provide a valid consent. Additionally, the ERC would like to know the percentage of women that are likely not to have been consented during the antenatal care period and whether the study could still answer the question should they be excluded.

1.10. The protocol should provide further information on how KMC will be implemented, particularly in relation to mothers that did not pre-consent or did not have a normal delivery (i.e. C-section). Please indicate the processes that will be followed to, for example identify a surrogate within a 2 hours period, the provisions that will be made for relatives or friends (surrogates) to stay at the hospital, or for mothers who would like to participate in KMC and have had a C-section, what support measures will be provided, KMC be explained, etc. Given the burden on mothers (who are expected to care for their babies 20 hours per day), all measures should be taken to facilitate and support them in their role.

2. Study Instruments

NIL

3. Informed Consent Forms

3.1. The consent documents should address the potential benefits of the intervention. For example, how being close to the mother regulates heart rate and temperature, and reduces stress.

Preliminary Informed Consent Form:

3.2. The language proposed in the consent document should be modified. Telling a mother during antenatal care that her baby can die and that in spite of the best available treatment in the hospitals some babies will not survive will create anxiety, fears, and concerns. The study team is requested to use clinical language that is sensible and can be understood by lay persons (e.g. "sometimes we cannot save all babies")

3.3. Under "Risks" it is specified "KMC is standard practice and does not have any known side effects for the mother or the baby". This is misleading as it applies to KMC initiated after stabilization of the neonate. However, it cannot be stated for babies who are unstable. Please modify.

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 a clarification, and it may not be mandatory for you to make changes to your protocol. Please consider the comments of the ERC and determine if you believe change is needed. If no change is made, the ERC will consider the response. If the judgement of the ERC is that a change should occur, the ERC will promptly notify you.

NIL

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

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – HTTP://WWW.WHO.INT/ETHICS/REVIEW-COMMITTEE/EN/ – HTTPS://EXTRANET.WHO.INT/ERCWEB/LOGIN.PHP

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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.*

Chairperson .... (Antonella Lavelanet) **Date**...21/06/17...

Name: Nigel Rollins

FINAL APPROVAL	**FOR THE SECRETARIAT**
Amendments and Clarifications to the proposal have been reviewed. The protocol (Version: 3 Date: 30.09.17) and informed consent Forms (Dated: 02.10.17) submitted on ..06.10.17........... are approved by the ERC **Chairperson** A.K. .... **Name** NR/KF ....K. Fernandez.... **Date** ....6/10/2017....	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 NA Relevant Documents submitted on NA Comments: NA Signature Date 06/10/17