WORLD HEALTH ORGANIZATION
Maternal, Newborn, Child and Adolescent Health Department

STUDY 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.

Short title: Immediate KMC study.

Protocol version

Version	Key changes		Date
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Executive Summary

Background: Globally about 15% of newborns are low birth weight (LBW), as a result of preterm birth or intrauterine growth restriction or a combination of the two, and up to 70% of neonatal deaths occur in these newborns. A recently updated Cochrane review reported a 40% reduction in mortality with KMC compared with standard care in hospitalized infants with birth weight <2.0kg. However, based on the time of initiating KMC in studies included in the review, about two thirds of low birth weight babies would have died *before* KMC was initiated. Thus, the 40% mortality impact of KMC in enrolled infants would only translate in practice to about 13% impact on neonatal mortality in all babies with birth weight <2.0kg. The impact of KMC on neonatal mortality could be much larger if it could be initiated immediately after birth and was effective.

Aim and hypothesis: The aim of this trial is to evaluate the safety and efficacy of continuous KMC initiated immediately after birth for neonates' with birth weight from 1.0 to <1.8 kg compared to the current recommendation of initiating continuous KMC after stabilization. The main hypothesis is that neonates with birth weight 1.0 to <1.8 kg, who are exposed to continuous KMC initiated immediately after birth, will experience a reduced risk of death compared to neonates in whom KMC is initiated after stabilization.

Methods:

Study design and setting: The study will be a multi-country, multi-centre, randomized controlled trial. The study will be conducted in tertiary care hospitals in five low- and middle-income countries in Asia and Sub-Saharan Africa, namely Ghana, India, Malawi, Nigeria and Tanzania.

*Sample size***:** The sample size for comparison of risk of death in intervention and control groups (21.1% compared with 16.8%) is 2080 per group, requiring a total of about 4200 neonates. Based on the number of neonates born in the selected hospitals, enrolment can be completed in about two years. For sample size calculation, we have conservatively assumed that the intervention group will have 20% lower mortality compared with control group.

*Population***:** The study population will be neonates born within the participating hospitals with birth weight between 1.0 and <1.8 kg, regardless of their gestational age. Babies will still be eligible if they are twins, or are born through caesarean section or if their mothers had delivery complications that are expected to resolve within 3 days, so that they will be able to move to the neonatal unit within 3 days of birth to provide KMC to the neonate. Triplets or quadruplets, or babies who are unable to breathe spontaneously within the first hour after birth, or who have congenital malformations that interfere with the intervention, or babies whose mothers are not able to give consent or refuse to participate in the study, or who live outside a defined study area will be excluded from the study.

*Intervention***:** The intervention has three main components (i) continuous skin-to-skin contact initiated immediately after birth with mother, aiming for at least 20 hours per day; (iii) promotion and support for early exclusive breastfeeding, and (iii) provision of health care for mother and baby with as little separation as possible. If the mother cannot provide continuous KMC for any reason, she will be asked to choose a surrogate to provide skin-to-skin contact.

The intervention group will be provided continuous KMC before stabilization in the neonatal special care unit, and continuous KMC after stabilization in the KMC ward.

*Comparator***:** Neonates randomized to the control group will receive conventional care, for which the mother and baby are separated, until the baby is clinically stable. Short sessions of KMC will be started in neonates randomized to the control group when the baby is recovering but is still in the special newborn care unit. Continuous KMC will be initiated after the baby is stable and is transferred to the KMC ward.

Care in both intervention and control groups: All neonates enrolled in this study will receive the WHO minimum package of care for small babies. This care will be the same for the intervention and control groups, except that babies randomized to intervention will be given continuous KMC with mothers or surrogates in the neonatal special care unit, but babies allocated to control group will receive care in incubators, radiant warmers or cots while they are unstable.

Outcomes: The primary outcomes of this study will be (i) mortality between enrolment and 72 hours of age, and (ii) mortality between enrolment and 28 days of age. Secondary outcomes will be time to stabilization, hypothermia and risk of infection during hospital stay, time to hospital discharge, exclusive breastfeeding at the end of neonatal period, maternal satisfaction with care received in the hospital, and maternal depression. We will also monitor mortality in the first 72 hours of life among all live births with birth weight between 1.0 and <1.8 kg in participating hospitals, irrespective of enrolment in the trial.

List of acronyms

CPAP: continuous airway positive pressure
DSMB: Data Safety Monitoring Board
ERC: Ethics review committee
iKMC: Immediate KMC
KMC: Kangaroo Mother Care
LMP: last menstrual period
PI: principal investigator
SCNU: special neonatal care unit
TAG: Technical Advisory group
WHO: World Health Organization

Introduction

Globally about 15% of newborns are low birth weight (LBW), as a result of preterm birth or intrauterine growth retardation or a combination of the two; and 60 to 80% of neonatal deaths occur in these newborns[1-3]. The causes of death of LBW neonates include respiratory and brain immaturity, hypothermia, hypoglycaemia, and infection[4,5]. In addition, LBW infants are at a high risk of impaired growth and development. A recent review of available interventions suggested that breastfeeding, hygiene, antenatal corticosteroids to prevent preterm birth complications, case management of suspected infections and hospital care of small babies including Kangaroo Mother Care (KMC) are the most effective interventions for improving survival of LBW infants[6]. WHO defines KMC as the care of preterm and LBW infants where the mother keeps the baby in skin-to-skin contact on her chest between her breasts continuously until the baby no longer wants to stay in that position, and exclusively breastfeeds the baby. This is because a preterm baby has immature temperature regulation, therefore baby may lose body heat very rapidly after birth and become hypothermic. This happens most often on the first day of life. Hypothermia in premature infants increases its metabolic need, oxygen consumption and is associated with increased morbidity and mortality. To protect the preterm babies from heat loss, they need to be kept in thermos-neutral environment, which can be provided by incubators, radiant warmers or by skin-to-skin contact. Incubators need not only high investment and maintenance but also are associated with high rates of infection due to high temperature and humidity inside the incubator, cause high noise, light and electromagnetic fields exposure to the babies inside, and can occasionally be associated with malfunctioning leading to over or under heating or other accidents. On the other hand, KMC is not only an effective way to keep a small baby warm, but it also promotes breastfeeding, reduces risk of neonatal infection, reduces the occurrence of apnoeic attacks and irregular breathing, increases mother's confidence in handling her small newborn baby, improves bonding, and reduces the cost of health care. There is evidence that KMC reduces mortality, possibly by the following mechanisms:

- KMC helps a preterm newborn to reach the stable body temperature faster than an incubator. While on KMC, the body temperature of a preterm is better maintained with lesser variation. When the body temperature is maintained, the preterm baby can use its energy for catch up growth.
- When the baby is in skin to skin contact with the mother, earlier initiation of breastfeeding is facilitated, and breastfeeding is continued longer. This decreases the chances of infection that would be introduced by unclean water used for the preparation of feeds or by lack of hygiene. Breast-milk also provides the baby with the immunity required to fight infections better.
- As mother is the main care giver for her baby, therefore it reduces the contact of the baby with the other health care staff and reduces the risk of cross-infection. The baby is more likely to colonized by mothers protective microbiome because of breastfeeding and contact with her.
- KMC promotes one to one care to these high risk babies, which is a very important advantage in these countries where the number of health care staff is very limited and the nurse to baby ratio is very low.
- The breathing of the mother regulates and stimulates the breathing of the baby and reduces the apnoeic attacks common in preterm babies.
- KMC promotes bonding of the mother baby dyad and makes the mother feel more confident in taking care of her small baby.

"*Kangaroo mother care: a practical guide*" provides guidance to initiate short KMC sessions when the baby starts to recover, even if the baby still requires medical treatment such as IV fluids or low concentration of additional oxygen. However, it is recommended that continuous KMC should be initiated only after the baby is stable; meaning that the baby must be breathing spontaneously without additional oxygen[7]. "*WHO recommendations on interventions to improve preterm birth outcomes*" recommends KMC for the routine care of newborns weighing 2.0kg or less at birth, which should be initiated in health care facilities as soon as the newborns are clinically stable. These babies should be provided as close to continuous KMC as possible. Intermittent KMC, rather than conventional care, is recommended for newborns weighing 2.0kg or less at birth, if continuous KMC is not possible[8]. There is no current recommendation for KMC for unstable <2.0kg neonates. A recently updated Cochrane review reported 40% lower mortality in infants with birth weight <2.0kg who were given KMC than mortality in those who were given standard (conventional) care in hospitals at 40-41 weeks postmenstrual age (3.2% vs 5.3%; RR 0.60, 95%CI 0.39 to 0.92; eight trials, 1736 infants)[9]. This review also showed a 65% relative reduction in the occurrence of nosocomial infections or sepsis at 40-41 weeks gestational age (RR 0.35, 95%CI 0.22 to 0.54; 5 trials, 1239 infants), a shorter duration of hospital stay and a higher prevalence, duration and exclusivity of breast feeding[10]. In almost all studies included in the Cochrane review, KMC was initiated after the baby was clinically stable. The median age at initiation of KMC was 3.2 to 24.5 days for most studies, see Table 1 below. Only in one study, was KMC initiated before stabilization at a median age of 10 hours[11]. This implies that over two-thirds of deaths among preterm babies would have occurred by the time these infants became stable enough to be provided KMC[12].

Table 1: Average age of enrolment to KMC in the Cochrane review (Conde-Agudelo 2016)

Studies reporting impact on mortality	Age at enrolment of participants
Acharya 2014[13]	No data on age
Boo 2007[14]	24.5 days
Cattaneo 1998[15]	10 (1 to 74) days
Charpak 1997 [16]	4 (1 to 60) days
Eka Pratiwi 2009[17]	No data on age
Ghavane 2012[18]	14.1 ± 10.3 days
Kadam 2005[19]	3.2 (1 to 8) days
Rojas 2003[20]	19 days
Sloan 1994[21]	13.0 ± 10.5 days
Suman 2008[22]	3.7 ± 2.8 days
Whitelaw 1988[23]	16 (1 to 66) days
Worku 2005[11]	10 hours

KMC cannot have an effect on deaths that happen before its initiation. Thus, the 40% mortality impact of KMC in enrolled infants would only translate in practice to about 13% impact on mortality in all babies with birth weight <2.0kg. The impact of the KMC intervention could be much larger if it could be initiated immediately after birth, and if it would have the same benefits as those when started after stabilization. Although there is a WHO recommendation for newborns without complications to be kept in skin-to-skin contact with their mothers

during the first hour after birth to prevent hypothermia and promote breastfeeding[24], this recommendation is rarely followed for babies with birth weight <2.0kg because they are considered to be clinically unstable and are quickly transferred to newborn special care units. The effect of continuous skin-to-skin contact starting immediately after birth on mortality in infants <2.0kg has not been evaluated. However, two small randomized controlled trials (RCTs) have evaluated the feasibility, safety, and effect on stabilization of initiating KMC immediately after birth. In the RCT from South Africa[25], skin-to-skin contact from birth was associated with 100% stability scores in the fifth to sixth hour of life as compared to 46% in the conventional care group in newborns weighing 1.2–2.2kg. Neonates managed in thermo-controlled incubators were significantly more hypothermic in the first hour, and had lower temperatures throughout the 6-hour observation period than those who received KMC immediately after birth (Bergman, 2004). A similar RCT from Vietnam in neonates weighing 1.5-2.5kg reported significantly better transition to extra-uterine life ($p < 0.02$) in the immediate skin-to-skin contact group. The neonates in the intervention group had significantly lower need for respiratory support, intravenous fluids, and antibiotic use during their hospital stay in this study[26].

We therefore propose to conduct a multi-country randomized controlled trial to evaluate the safety and efficacy of continuous KMC initiated immediately after birth for very small babies compared to starting continuous KMC after stabilization. This intervention will be implemented in the context of improving care for both intervention and control groups by implementation of the WHO minimum package of care for small babies (warmth, hygiene, breast-milk feeding, and if required intravenous fluids, parenteral antibiotics, oxygen, continuous positive airway pressure, and monitoring). This study will address one of the important research priorities for improving newborn survival. This question is most relevant to health facilities in resource-limited settings where the mortality among low birth babies is high.

Research question:

In babies with birth weight 1.0 to <1.8 kg (**P**opulation), what is the effect of continuous KMC initiated immediately after birth (**I**ntervention) compared to current practice of initiating continuous KMC after stabilization(**C**omparator) on their survival (**O**utcome)?

Objectives:

The primary objective is to measure the effect of continuous KMC initiated immediately after birth on post-randomization mortality during the first 72 hours of life and during the neonatal period, compared with continuous KMC initiated after stabilization, in infants with birth weight 1.0 to <1.8 kg born in hospitals of low- and middle-income countries.

The secondary objectives are to determine the effect of the intervention on time to stabilization, risk of hypothermia, risk of infection during hospital stay, weight gain, time to hospital discharge, time taken to reach full breastfeeding, and exclusive breastfeeding at the end of neonatal period.

Study design:

The study will be a multi-country randomized controlled trial. The unit of randomization will be mother-baby pair and the study will have two parallel groups with one to one allocation. Statistical power will only be achieved in combined analysis of data from all countries, i.e. this will be a multi-centre study. Blinding is not possible due to the nature of the intervention. However since the primary outcome is mortality and therefore measurement bias is unlikely, especially when loss to follow up is very low and an intention to treat analysis is performed.

Methods

Study settings:

The study will be conducted in five tertiary level hospitals in low-resource countries of Asia and Sub-Saharan Africa including Ghana, India, Malawi, Nigeria and Tanzania. These hospitals serve as referral centres which provide care to sick and small babies referred from other hospitals. These hospitals therefore have a high proportion of preterm and small for gestational age babies, also because women with complications are frequently referred to these hospitals from smaller health facilities.

In all these hospitals, babies with birth weight <1.8 kg are routinely separated from the mother just after birth and provided care in special care newborn units. Care provided in the special care newborn units includes warmth, breast-milk feeding, and if required, intravenous fluids, parenteral antibiotics, oxygen, and continuous positive airway pressure. There is no or limited access to more sophisticated interventions such as surfactant therapy and mechanical ventilation in most hospitals. KMC is practiced in all these hospitals after achieving stabilization, usually after 3-7 days of age. However, the coverage and quality of KMC implementation is variable across sites. Review of records from participating hospitals for the past year shows that the number of infants born with birth weight 1.0 to <1.8 kg, varied between 250 and 1500 in different hospitals. See Annex 1 for a description of individual study sites.

Population:

The study population will be live neonates, born within the participating hospitals, with birth weight 1.0 to <1.8 kg. Inclusion based on birth weight (as opposed to gestational age) is considered the best option to select the target population for three main reasons: (1) accurate gestational age estimation is unlikely in study settings where the ascertainment of the date of last menstrual period (LMP) is generally not accurate and very few women have an ultrasound in early pregnancy; (2) there is high incidence of small-for-gestational-age babies who are also at a high risk of death and could benefit from skin-to-skin contact; (3) it is relatively easy to have accurate measurement of birth weight. Babies with birth weight below 1.0 kg have low chances of survival even in high-resource settings with sophisticated neonatal intensive care. The intervention would be difficult to implement in babies with extremely low birth weight. Babies with birth weights 1.8 kg or more are likely to be stable at or within the first hours after birth and therefore should not be separated from their mothers and provided KMC based on current recommendations.

Inclusion criteria

All babies born alive in the participating hospitals, with birth weight between 1.0 to <1.8 kg, regardless of their gestational age, are eligible for participation in this trial with their mothers. The mother-baby pair is still eligible if the mode of delivery is caesarean section, if the babies are twins or if the mother experiences some complications during labour and delivery that are expected to resolve within 3 days.

Exclusion criteria

This trial will exclude mother-baby pairs if any of the following is present:

(i) the mother is younger than 15 years of age
(ii) the mother (or her guardian in case mother is a minor aged 15-17 years) is unable or unwilling to provide consent;
(iii) the mother is unlikely to be able to provide KMC for the first 3 days after birth, e.g. she has eclampsia, shock or has undergone major surgery;
(iv) the baby is unable to breathe spontaneously within 1 hour of birth;
(v) multiple pregnancy: triplets or more;
(vi) the baby has a congenital malformation that interferes with the intervention, or the intervention interferes with the required care for the congenital malformation;
(vii) the place of residence is not a part of the defined study area (the study area will be defined to make 28-day follow up home visit feasible)
(viii) If for any reason the mother baby pair cannot be enrolled within 2 hours of birth of the baby.

Intervention

In this study, KMC is defined as continuous skin-to-skin contact with mother or her surrogate aiming for at least 20 hours per day, support for exclusive breastfeeding, and required medical care without separation from the mother as much as possible. The three components of the intervention are described in greater detail below.

Continuous skin-to-skin contact initiated as soon as possible after birth

Continuous skin-to-skin contact will be initiated immediately after randomization, as soon as feasible after birth, aiming for at least 20 hours a day . This will be initiated by the mother or the surrogate within the delivery room or the operation theatre, and continued during transfer to special care newborn unit (SCNU), and continued during the stay in the SCNU. Mother and baby will be kept in the neonatal unit until the baby meets stability criteria. After stabilization, mother-baby pair will be shifted out from the newborn unit to KMC ward, and continuous KMC will be provided there until discharge from the hospital. All interruptions of skin-to-skin contact will be noted and baby and mother will receive care as per hospital protocol. At the time of discharge, the mother will be advised to continue KMC at home.

Health care for mother and baby provided without separation:

In the intervention group, the mother and baby will remain in skin-to-skin contact from the time of randomization. The mother and baby will be provided health care without separation as much as possible. Mothers will be provided health care by obstetric staff while she is in the neonatal unit. If a mother has any complication for which she needs to be transferred to the postnatal ward, intensive care unit or operation theatre, skin-to-skin contact will be continued with a surrogate.

If the baby requires a procedure or treatment that is not possible in skin-to-skin contact, the baby will be shifted to a cot or radiant warmer. skin-to-skin contact will be temporarily interrupted for the period of the procedure or treatment, and recommenced as soon as possible after that.

If both the mother and surrogate are temporarily not available to provide KMC in the SCNU, the baby will be kept in a cot, incubator or radiant warmer as required.

Promotion and support for early and exclusive breastfeeding

Mothers will be encouraged and supported to put the baby to the breast when they are in the SCNU. Even if the baby is unable to feed from the breast, putting the baby to the breast provides the baby the opportunity to learn how to attach and suckle. Continuous skin-to-skin contact between mother and baby is likely to facilitate breastfeeding. A breastfeeding counsellor will be available at all sites to help the mothers solve breastfeeding problems they face.

How will high compliance with KMC be achieved?

Formative research in each site will be conducted to identify barriers to deliverability and acceptability of the intervention, and to develop and test solutions to overcome them. Formative research will be carried out in the hospitals on women who have delivered a small baby in the hospital, and on their family members. All hospitals are providing KMC to such babies after they are stable. The following four questions will be addressed:

1. How can the mothers be given appropriate care and comfort while they are stationed in newborn special care units to provide KMC to their infants?
2. Who are the women who are appropriate and acceptable as surrogate to mothers for providing KMC in each site according to their culture? What are the factors that must be taken into consideration while selecting a surrogate to a mother for providing KMC to her baby?
3. What are the challenges that the mothers face in providing round the clock skin-to-skin contact to their babies and how can they be resolved?
4. What is the best time for the women to receive information about the study, and for them to provide consent?

All efforts towards building a KMC conducive environment for mothers and families will be made. These include beds or reclining chairs for mothers, appropriate clothing, food, toilets and other requirements for making the mothers comfortable.

KMC research assistants will encourage and support mothers to safely keep the baby in skin-to-skin contact, and support breastfeeding. This support will be provided to intervention group mothers from the time of randomization, and to the control group mothers after the baby is allowed to initiate KMC by the treating clinician based on current WHO guidelines.

All mothers will be closely supported by the study KMC support worker. This support will comprise of three main components – counselling on KMC, making the mother and/or surrogate comfortable and support for breastfeeding. Counselling will include explanation and demonstration of the method of providing skin to skin contact, the importance of KMC to the baby and ways to comfortably provide KMC. The most important factor for successful implementation of the intervention is keeping the mother comfortable. This includes among other things, taking care of her pain, comfortable bed, toilet, food and water, and a soothing environment. Breastfeeding support will include counselling on the importance of early and exclusive breastfeeding, and support for appropriate positioning and attachment. The worker will also counsel the mother on how to cope with the fact that she has had a low birth weight baby.

At the time of consenting, the mother will be asked to name a surrogate who could provide KMC when the mother is unable to do so. The KMC support worker will ensure that the surrogate is not only allowed to stay in the hospital and in the special newborn care unit, but also has access to food, toilet and other basis services. All participating hospitals will make policy adjustments for this to happen.

Comparator

Neonates randomized to the control group will receive conventional care, and the mother and baby will be separated until the baby is clinically stable. Mothers will be admitted in postnatal ward and babies will be admitted in the SCNU. When feeding can be started based on the clinical condition of the baby, expressed breast milk will be given using a feeding tube or cup and direct breastfeeding will be started when the baby is ready. Except for the time of initiation of KMC, all the other medical care will be same for intervention and comparison groups.

Short sessions of KMC will be started for neonates randomized to the control group when the baby is considered to be recovering, and is at least 24 hours old. The criteria to consider a baby recovering include:

- CPAP not required
- SpO2 90-94% on low concentration of additional oxygen (FiO2 $\leq$30% by nasal prongs)
- Tolerating partial enteral feeds (maybe on partial IV fluids)

The mother will come to the SCNU to provide these brief sessions of KMC a few times a day.

Continuous KMC will be initiated for a baby randomized to the comparison group when the baby meets stability criteria. They will be transferred to KMC ward before continuous KMC is

initiated. A baby will be considered to be stable when the following criteria are met for at least a continuous period of 24-hours:

(i) Breathing spontaneously without additional oxygen, and oxygen saturation on room air >90%
(ii) No need for CPAP
(iii) Respiratory rate 40 to <60 breathes per minute
(iv) No apnoea
(v) Heart rate 80 to <180 beats per minute
(vi) Axillary temperature 36.0 to 37.4°C
(vii) No need for intravenous fluids

The comparison group will differ from the intervention group as they will not receive continuous KMC from the time of randomization until all stability criteria are met. Continuous KMC will only be initiated in the comparison group babies when they are transferred to the KMC ward after stabilization. Both groups will receive exclusive breast milk feeding, as far as possible.

Care of newborns in both intervention and control groups

All neonates included in this study will receive health care as per the hospital policy, and WHO guidelines. The same health care will be provided for intervention and control groups, except that the intervention group will be on continuous KMC with mothers in SCNU, and control group babies will be placed in incubators, radiant warmers or cots.

All participating hospitals will be supported to make quality of care improvements, so that they can implement the WHO minimum package of care for small babies more effectively. The WHO minimum package of care includes: monitoring, thermal control, breast-milk feeding support and attention to hygiene for all babies. It also includes: access to intravenous fluids, antibiotic therapy and respiratory support with safe oxygen supplementation and bubble CPAP, if required.

Monitoring of enrolled newborns

Currently, there is variability in monitoring schedules across hospitals. The study will upgrade the level of monitoring and make it consistent across hospitals. Every newborn in the SCNU will be monitored and information recorded every 6 hours for temperature, heart rate, respiratory rate, oxygen saturation. The study will procure pulse oximeters for monitoring of heart rate and oxygen saturation to make sure that they are available for all participants. Blood sugar will be monitored every 6 hours during the first 24 hours after birth. In KMC ward, babies will be evaluated every 12 hours up to hospital discharge. At any monitoring visit showing clinical deterioration, the diagnosis of possible serious bacterial infection will be considered. The table below describes the minimum routine monitoring schedule.

Table: Monitoring schedule in neonatal unit and KMC ward

In SCNU (every 6 hours) in <u>unstable</u> babies in both intervention and control groups		**In KMC ward (every 12 hours) in <u>stable</u> babies in both intervention and control groups**	
Measurement	***Method***	***Measurement***	***Method***
Axillary temperature	Clinical thermometer	**Axillary temperature**	Clinical thermometer
Respiratory rate	Observe and count breaths for one minute	**Respiratory rate**	Observe and count breaths for one minute
Heart rate	Pulse oximeter	**Heart rate**	Auscultate and Count for 30 seconds and multiply by two
Respiratory distress	Observe for chest indrawing, nasal flaring, and grunting	**Respiratory distress**	Observe for chest indrawing, nasal flaring, and grunting
Oxygen saturation	Pulse oximeter		
Blood glucose (during first 24 hours after birth)	Blood glucose test strips		

Care for mothers

Unstable mothers or mothers who require special care will not be transferred to SCNU. They will continue to be managed in the intensive care unit or postnatal ward, as per usual hospital practice. They will only be transferred to SCNU for providing KMC when they no longer require special care.

Obstetric staff will be responsible to provide postpartum monitoring and care for all mothers. If a mother is allocated to intervention, she will receive routine postnatal care in the neonatal unit. Postnatal care to a woman who is part of the control group will be provided in the postnatal ward. The SCNU nursing staff will provide support in case of any emergency (such as secondary postpartum haemorrhage) and contact the obstetrics staff to provide definitive care. The research assistant responsible for supporting KMC will also assist the mother to get emergency care rapidly.

Outcomes

The primary outcomes of this study are mortality between enrolment and 72 hours, and mortality between enrolment and 28 days of age. Secondary outcomes are related to stabilization, breastfeeding, risk of infection, hypothermia and hypoglycaemia. All outcomes will be measured using identical methods in intervention and control groups by an independent outcome measurement team, which will not be involved in the delivery of the intervention. The primary and secondary outcomes are presented in the table below.

Table: Description of study outcomes of interest

Primary outcomes	**Description**	**Measurement strategy**
A. Death between enrolment and 72 hours of age	Death of an enrolled neonate occurring any time between enrolment and 72 hours of age.	Vital status recorded every 12 hours during hospital stay (enrolled baby unlikely to be discharged before 72 hours of age)
B. Death between enrolment and 28 days of age	Death of an enrolled neonate occurring any time between enrolment and 28 days of age.	Vital status recorded every 12 hours during hospital stay, and at a home visit on day 29 of age.
Secondary outcomes	**Description**	
Exclusive breastfeeding (or exclusive breast milk feeding) at the end of the neonatal period.	Exclusive breastfeeding is defined as an infant receiving only breast milk and no other liquid or solid, with the exception of vitamin or mineral supplements, medicines or ORS, if prescribed.	24 hour feeding recall at a home visit on day 29 of age.
Time to being fully breastfed	Age at which the baby could feed fully by suckling on the breast, without requiring any feeding by cup or nasogastric tube.	Mode of feeding recorded every 12 hours during hospital stay
Suspected sepsis Early onset: <72 hours of age Late onset ≥72 hours of age	Sepsis will be suspected when a baby has clinical deterioration after initial improvement. This includes stopped feeding well after starting to feed, increase in respiratory distress after initial improvement, lethargy after improvement in activity, fever, or hypothermia after baby started maintaining temperature (not associated with environment hypothermia or with hypoglycemia).	Clinical signs recorded every 12 hours during hospital stay
Probable sepsis, early or late onset	Criteria for suspected sepsis met, plus a positive laboratory screening test (high or low neutrophil percentage and count or positive C-Reactive Protein)[27]	Neutrophil count and CRP if clinical criteria for suspected sepsis are met
Hypothermia	Any instance of axillary temperature <36°C from 2h after randomization until discharge (or 28 days of age if not discharged until then).	Temperature recorded every 12 hours during hospital stay

Hypoglycemia	Any measure of blood glucose <45 mg/dl (2.6mmol/l).	At mandatory measures at 6, 12, 18 and 24 hours of age, or at any other time if needed.
Time to clinical stabilization	Age at which the baby is considered to be clinically stable. The following criteria for stability should be met for at least a continuous period of 24 hours: (i) Respiratory rate 40-60/min (ii) No apnoea (iii) No need for CPAP (iv) SpO2 on room air >90% (v) Heart rate 80-160/min (vi) Axillary temperature 36-37.4°C (vii) No need for IV fluids	Clinical signs and health care recorded every 12 hours during hospital stay
Death in babies not enrolled in the study up to 72 hours of age	Death between birth and 72 hours of age of a neonate born in the hospital who had a birth weight between 1.0 to<1.8kg but could not be enrolled in the study.	Hospital mortality data for all babies with birth weight between 1.0 to<1.8kg who died before screening, or had an exclusion criterion.
Maternal satisfaction with health care in the hospital	Satisfaction with health care received by the mother and baby.	Questionnaire to the mother after transfer to KMC ward, and around the time of discharge from the hospital.
Maternal depression	Patient Health Questionnaire 9 (PHQ-9) score of 15 points or more.	PHQ-9 administered to mothers at the day 29 home visit (Kroenke 2011).

In addition to primary and secondary outcomes, two important ***process outcomes*** will be measured:

Compliance with KMC: A daily sheet will be completed by the research assistant in the SCNU and KMC ward. This sheet will have an hourly record of duration of skin-to-skin contact with the mother or the surrogate, and the period of separation. This includes the brief KMC sessions that control group babies may receive in the SCNU. The number of times the baby is put to the breast will also be recorded. At the home visit on day 29, mothers will be asked if KMC was continued after discharge from hospital.

Duration of hospital stay: The age of the baby at discharge from hospital will be recorded in the discharge form.

Sample size

Preliminary data from the five selected sites shows that neonatal mortality among neonates with birth weights between 1.0 and 1.8 kg was about 32% in 2015. After improved implementation of the WHO recommended minimum package of care for low birth weight infants in these hospitals, we expect that the mortality during the study period in the control group will fall by about one third, to be about 21%.

The following assumptions were used for sample size calculation:

- Mortality in the control group: 21%
- Expected mortality in the intervention group: 16.8% (20% lower than control group)
- Significance level: 5%
- Power: 90%
- Maximum loss to follow up: 10%

The sample size for comparison of two proportions (21.0% compared with 16.8%) is 2080 per group, thus a total of 4200 neonates will be required to be enrolled. Based on the number of neonates born in the selected hospitals, and assuming that we will be able to enroll about half of these births, enrolment can be completed in about two years.

COUNTRY/SITE	Eligible 1.0-1.8kg infants	Expected enrolment per month	Expected enrolment in 2 years
Ghana	50	25	600
India	140	70	1680
Malawi	50	25	600
Nigeria	30	15	360
Tanzania	80	40	960
Total	350	175	4200

Ethical considerations for this study

High mortality risk participants

As stated earlier, a review of records shows that the mortality of babies with birth weight of 1.0 to <1.8 kg, in participating tertiary care hospitals, is very high. Overall about a third of these babies do not survive the neonatal period. We therefore believe that research, such as the current study, that may lower mortality is of paramount importance in these hospitals. The two RCT's on KMC described above[25] and ongoing studies in Sweden and Norway have shown that immediate KMC is safe, and an effective method of reducing mortality in small babies. The techniques used in these previous studies such as securing with a binder to keep the head slightly extended, will be implemented in the current study.

Although all these hospitals are implementing the interventions in the WHO minimum package of care, the quality of implementation of these interventions is variable across sites.

The study will have concrete activities to improve the delivery of the WHO minimum package of care at these hospitals. This will improve survival in both intervention and control babies. The study will support training using the package *Essential Care for Small Babies* for all relevant health care staff. Two key specific gaps in care are respiratory support, particularly effective and safe CPAP, and regular and mandatory monitoring. These gaps will be covered by procuring adequate number of safe CPAP machines and pulse oximeters for all hospitals using study funds, and having standard operating procedures for the use of this equipment.

Health care for study participants

All enrolled infants will receive the same health care, with the exception of continuous KMC which will be started immediately after randomization for the intervention group and after stabilization in the control group. This care will include warmth, hygiene and breast-milk feeding for all babies. Intravenous fluids, antibiotics, oxygen and CPAP will be given for those babies who need them. The study team will provide training for health care staff in implementing the WHO minimum package of care for small babies. The study will also procure safe CPAP machines with oxygen concentrators, and pulse oximeters in adequate numbers to improve quality of health care in participating hospitals.

Health care for mothers

Mothers who provide KMC in the neonatal unit will receive the same postpartum care as mothers of infants in the control group. Since these mothers will physically be some distance away from the postnatal ward, the research team will establish additional protection mechanisms to ensure that mothers in the neonatal unit will have the same access to obstetric care as controls. The SCNU staff will assist the mothers for their needs and in case of emergencies. The research assistant in the SCNU will complete on daily checklist to ensure that the mothers have received their postnatal visits. The research assistant will also help in getting immediate access to health care in case of any emergency.

Care of twins

Twin babies will not be given different care or be separated from the mother because of the study. If both twins are eligible for enrollment, they will be allocated to the same group. If allocated to control group, both babies will be kept in incubators or radiant warmers, and continuous KMC will be initiated only after they become stable. If allocated to intervention group, both babies will be kept in skin-to-skin contact with mother and/or surrogate.
If only one of the twins is eligible for the study (e.g. the other has weight <1kg or ≥1.8kg), and this baby is allocated to control group he/she will be cared for in the SCNU, while the other twin will be with the mother at postpartum ward or in the SCNU. Alternatively, if the eligible twin is allocated to intervention then he/she will be cared for in the SCNU with the mother/surrogate, while the other non-eligible twin will be in the postnatal ward or in SCNU. If the second baby does not require admission to SCNU, the mother will decide which twin will be cared for by her and which one will be cared for by the surrogate at different times.

State of the mother and provision of informed consent

An important ethical issue is that mothers will be asked to provide consent for participation when they are in a difficult situation, i.e. in the minutes and hours before and after birth. The

nature of the intervention (starting KMC as soon as possible after birth) and the eligibility criteria (birth weight 1.0 to <1.8 kg and no exclusion criteria) mean that the final confirmation of consent needs to be taken in the minutes after birth. The process of providing information about the trial to mothers and taking their consent for participation is described below.

Pregnant women attending antenatal care clinics in the participating hospitals will be given a printed sheet providing information about the trial if they are found to have a risk factor for having a low birth weight baby.

All pregnant women admitted in hospital for childbirth in labor or before caesarean section will be screened for the risk of delivering a low birth weight baby. If a mother is likely to deliver a low birth weight baby, a research assistant will provide all the information about the study and seek her consent for participating in the study. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physicially, psychologically and emotionally fit to provide consent. After birth of the baby, if all the inclusion criteria are met and none of the exclusion criteria are present, the consent of the mother will be verbally confirmed.

In situations where a baby is born unexpectedly very small, the research team has no alternative but to obtain consent from mothers just after delivery. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physicially, psychologically and emotionally fit to provide consent. Previous studies have successfully taken consent of women when they were admitted during labor or for childbirth as shown in the study for the treatment of postpartum hemorrhage[28] and for HIV testing[29]. We therefore feel that the mother will be able to provide consent within the first two hours of birth. However, these mothers will be given the opportunity to decide about continued participation in the trial 24 hours after birth.

Mothers who are minors will be eligible for enrolment in this study if they are at least 15years of age. Assent from the mother will be obtained before recruitment but the consent form will be signed by the minor mother's guardian (husband or parent).

If a woman is illiterate, an impartial witness will be present during the entire informed consent reading and discussion. The impartial witness will also sign and date the consent form, along with the individual who performed the informed consent discussion.

This study is to be conducted according to Ethical Guidelines for Research on Human Participants. The medical care given to, and medical decision made on behalf of Subjects will always be the responsibility of a Principal Investigator. Each individual involved in conducting the study shall be qualified by education, training and experience to perform his or her respective task(s).

Ethics approval

The study can only start at the Investigator's site when the relevant Ethics Committees have given, signed and dated approval of the protocol, written informed consent forms and other written information to be provided to the Subjects and Subject LAR.

Since this is a multi-country, multi-center study with a single protocol, approvals on the same protocol will be obtained from the WHO Ethics Review Committee as well as local Institutional Review Boards.

Study implementation strategy

Study teams

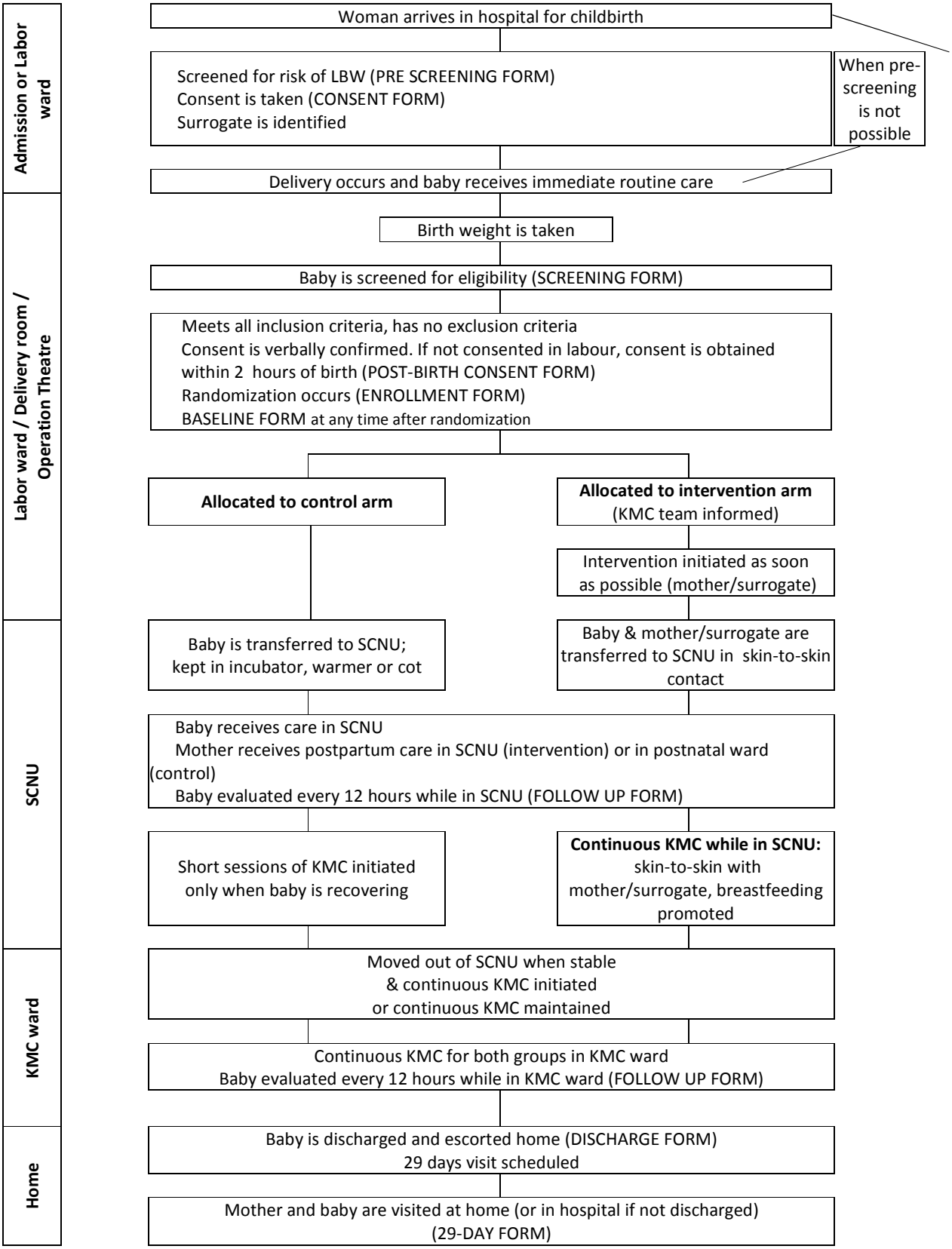
The study will be implemented in a standardized manner across all sites, coordinated by the WHO team. A full time site trial coordinator at each site will be responsible for the implementation of the trial. There will be three independent teams at each site that will implement different activities in the trial: (i) Screening and enrollment team; (ii) KMC support team; and (iii) Outcomes measurement team. Each team member will be trained in Standard Operating Procedures relevant for their work.

The s**creening and enrollment team** will be responsible for *pre-screening, consent, screening, post-birth confirmation of consent, enrolment and random allocation* to intervention and control groups, as well as taking re-consent 24 hours after birth from those who provided consent only after birth. Details of these activities are described in the sections below. At least one research assistant from this team will be available 24 hours by 7 days in admission area and in delivery ward. This research assistant will be available when a mother is admitted to the hospital for childbirth and when the birth occurs.

The **KMC support team** will be responsible for supporting *initiation of skin-to-skin contact* immediately after randomization in the delivery room, *transfer of the mother/surrogate and baby to SCNU in skin-to-skin contact, continue KMC while the baby is in SCNU* for the intervention group. This team will also support the control group with brief sessions of KMC when the baby is recovering in SCNU. In addition, continuation of KMC in the KMC ward will be supported for both the intervention and control groups. The team leader at each site will be a senior clinician who will coordinate the safe and effective implementation of KMC in the site. This team members will be trained laypersons who will be stationed in the SCNU, 24 hours a day and 7 days a week, and will visit the delivery room and KMC ward as and when required. These team members will help counsel the mothers for coping with the fact that they have had a low birth weight baby.

The **outcome measurement team** will be totally independent and separated from the previous two teams. Their tasks are to *measure outcomes from the time of randomization until discharge from the hospital*, and to make a *home visit to ascertain vital status on day 29* after birth. In addition, this team will collect *baseline and socio-demographic information* from all enrolled mothers. The facility based outcome measurement research assistants will visit SCNU and KMC ward every 12 hours and complete the follow up form. This will involve a review of the records, asking the mother/surrogate a few questions, and observing the baby. All evaluations will be shown to the doctors. An outcome measurement field assistant will accompany mother and baby home when discharged from hospital. A home visit to ascertain vital status will be conducted by the field assistant on day 29 after birth.

Study flow chart



Pre-screening

High risk pregnant woman will be informed about the trial at antenatal care visits to the participating hospitals. However, the process of pre-screening and consent will occur at the time the mother is admitted to the hospital for childbirth.

Participating facilities will have a research assistant present in the admission/delivery ward 24 hours a day and 7 days a week. Mothers admitted for childbirth, including those to be delivered by planned caesarian section, will be pre-screened if they are not in advanced stages of labor. A mother will be considered to be at high risk to deliver a small baby if at least one of the following conditions is met:

a. Last Menstrual Period dates suggest that at the time when the birth is expected the gestation would be <37 weeks
b. Early ultrasound suggests that at the time when the birth is expected the gestation would be <37 weeks
c. Intrauterine Growth Restriction based on ultrasound in 2nd or 3rd trimesters
d. Maternal age <18
e. Maternal height <1.50 m
f. Multiple pregnancy
g. Eclampsia or pre-eclampsia
h. Severe anemia (<7 g/dl)
i. Fundal height < 32cm

If any of the above conditions is met, a consent form will be administered.

Consent

All mothers considered to be at risk of delivering a small baby will be provided information about the study, and asked for consent for participation in the study in case they deliver a small baby who meets study eligibility criteria. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physicially, psychologically and emotionally fit to provide consent. The mothers will be asked to confirm their consent for participation in the study verbally within the first two hours after birth.

In situations where a baby is born unexpectedly very small, the research team has no alternative but to obtain consent from mothers just after delivery. Consent will be obtained within the first two hours of birth if the treating physician or nurse/midwife certifies that the woman is physically, psychologically and emotionally fit to provide consent. However, these mothers will be given the opportunity to decide about continued participation in the trial 24 hours after birth.

Minor mothers would be eligible for enrolment in this study if they are at least 15 years of age. Assent from minor mothers will be obtained for recruitment and informed consent from mothers' guardians (husband or parents) will be sought.

Every mother will receive full information about the trial, including potential risk and benefits of participation in the language of her choice. Her questions about the trial will be answered, and then she will be asked if she would be interested in participating in case she and her baby were eligible. Interested mothers will also be asked to identify 1-2 adult women relatives or friends of their choice who could act as their surrogates for providing skin-to-skin contact when the mothers are not able to do so. The informed consent form will be administered by the screening and enrolment research assistant.

If the pregnant woman is illiterate, an impartial witness will be present during the entire process of taking an informed consent. The impartial witness will also sign and date the consent form, along with the individual who performed the informed consent discussion.

If there is a refusal for participation in the study, the mother and baby will continue to receive standard care as per hospital protocols. Mother's will be made aware that even after providing consent, they will be free to withdraw from the trial at any stage, and in case they withdraw later , they and their babies will still continue to receive the same quality of care as required by any other patient with the same condition.

Consent from a surrogate will be taken only if the mother-baby pair is randomized to the intervention group.

Those mothers who could not consent for the study before the caesarean section will be excluded from the study.

Screening

Screening will be conducted in the delivery room or in the operation theatre by a screening and enrolment research assistant, who will be available 24 hours by 7 days. After birth, the mother and baby will receive the essential immediate care by the health staff. The baby's birth weight will then be taken by the health staff and the research assistant. If the weight is between 1.0 and <1.8 kg, the screening form will be completed to assess if the mother and baby meet all inclusion criteria and do not have any exclusion criteria. The eligibility criteria are described in the section on "Population" above. If mother and baby are eligible, the mother will be asked to confirm consent.

Enrolment

As soon as informed consent for participation is confirmed, the mother and baby will be enrolled, given a study identification number next in sequence for the stratum (see below) to which the baby belongs. If the mother-baby pair cannot be randomized within 2 hours after birth for any reason, the pair will not be enrolled in the study even if otherwise eligible.

Randomization

Sequence generation: A WHO statistician will prepare a computer-generated block randomization list with variable block size, stratified by site and by birth weight. The strata by birth weight will be from 1.0 to <1.5kg and from 1.5 to <1.8kg.

Allocation concealment: The random allocation will be concealed in serially numbered, opaque, sealed envelopes that will be prepared at WHO and sent to sites.

Implementation of randomization: After mother's consent is confirmed, and the mother and baby are enrolled and given the study identification number, the screening and enrollment research assistant will open the sealed envelope with that number which will have the group allocation inside. The research assistant will record the assignment of the mother and baby pair to intervention or control groups. The research assistant doing the enrolment will inform the KMC support research assistant about the allocation.

Initiation of care according to group allocation

If the baby is allocated to the intervention group, the KMC support research assistant will go to the delivery room or operation theatre to help the mother (or the surrogate in case the mother is indisposed) to initiate KMC as soon as possible after randomization. Monitoring of oxygen saturation and heart rate will be done using a portable pulse oximeter. The KMC support research assistant will also help to transfer the mother (or surrogate) and the baby to the SCNU in skin-to-skin contact. The research assistant will continue to support the mother or surrogate to provide continuous KMC after the baby is admitted in SCNU.

If the baby is allocated to control group, routine care will be provided by hospital staff. The baby will be transferred to the SCNU as soon as possible. When discharged from delivery room or operation theatre, mother will be transferred to postpartum ward and baby will remain in SCNU as per current guidelines. When the baby is ready to be fed, the mother will provide expressed breast milk. When the baby is recovering, the mother will provide brief sessions of KMC in the SNCU as per current WHO guidelines.

For providing KMC, the baby will be put naked on mother's chest between the breasts. The baby will have a cap, diaper and socks, and an open front shirt can be used in cold weather. The mother and baby will be in direct skin-to-skin contact with each other without any layer of clothing between them. The study will provide a special wrap that will secure the baby in a position where his/her neck is slightly extended while sleeping. The mother will wear loose clothing to cover both herself and the baby. They will both then be covered by a sheet or warm blanket depending on ambient temperature. The baby will be closely monitored by the mother and the research/hospital staff using a pulse oximeter when in KMC position. If the neonate needs interventions that cannot be safely or adequately provided in skin-to-skin contact, the neonate shall be moved to an appropriate area for doing so, and skin-to-skin contact will be re-established after intervention is provided. The neonate will be kept in skin-to-skin contact as much as possible, preferably with the mother but with a family member for the time the mother cannot provide the intervention. The interruptions in skin-to-skin contact will be documented in order to later calculate the duration for which the intervention was provided per day.

Trained nursing staff will provide support for exclusive breastfeeding, including appropriate positioning and attachment to the breast. A breastfeeding counsellor will be available at all sites to help the mothers solve breastfeeding problems they face.

Data collection

Outcomes will be assessed in the intervention and control groups by an independent research team using identical methods and procedures. This team will not be involved with intervention delivery. Outcome measurement during hospital stay will be through review of medical records (medical notes, treatment and feeding charts), interview with mothers, observation of the care given and assessment of the baby. The research team will visit SCNU and KMC ward every 12 hours. The results of the assessment will be shown to the health care staff for any necessary action. The outcome data collectors will be trained to follow Standard Operating Procedures and their performance will be supervised. If the mother is sleeping or busy with her baby, the contact with mother and the evaluation of the baby will be postponed.

All forms completed by the outcome measurement and screening and enrolment teams will be directly entered in an electronic platform. Data range and consistency checks will be incorporated into the data entry system. Facility based data collection will occur up to hospital discharge. When the baby is ready for discharge from the hospital, field assistants will accompany mother and baby home to get GPS coordinates of the house, as well as to confirm contact information and obtain any alternative address where she would like to stay, to facilitate last follow up visit. A home visit will be conducted on day 29 of age to ascertain outcomes at the end of the neonatal period.

Training and standardization

Health care staff in the delivery room, neonatal unit and KMC ward will be trained to provide the WHO minimum package of care for low birth weight babies using the *Essential Care for Small Babies* training package. All relevant staff of the neonatal unit and KMC ward, as well as the KMC support research assistants, will be trained to support KMC for very small babies. This will include how to secure them with the wrap to maintain the baby's head in a "sniffing position" in order to keep the airway open, particularly when the baby is sleeping.

All research assistants of the screening and enrollment, KMC support and outcome measurement teams will be trained in a standardized Manual of Operations for the study. The research assistants will also be trained on electronic data collection. All research staff will be trained in rapport building and communication with mothers and families.

Standardization exercises for assessment of clinical signs including respiratory rate, temperature, chest indrawing, grunting, nasal flaring and lethargy will be done, and continued until acceptable intra- and inter-observer variability is achieved.

Quality assurance

All three study teams (screening and enrollment, KMC support and outcome assessment) will have study supervisors who will support adherence to the manual of operations. Internal quality checks will be conducted by the trial coordinators and study Principal Investigators at each site. The two types of quality checks will be supervised observations and random independent checks. For the former each research assistant will be accompanied by the trial coordinator/PI for an activity each week. For the latter, 5% of observations will be independently checked by the trial coordinator/PI.

External oversight and support will be provided by WHO staff to ensure quality of study implementation. This will be done through site visits by WHO staff or consultants using a standardized monitoring checklist. Additionally, sites will transfer data to WHO every month and this data will be reviewed by WHO staff for quality, and feedback for improvement will be provided to the PIs.

Data management

A standardized database for the study will be created using a standard data platform such as RedCap or OpenClinica. The questions, response options, variable names and data structure will be identical for all sites. Each site will be responsible for data management and data safety. The data manager at each site will be responsible for data quality checks and query management, and for ensuring completeness of data. Any discrepancies will be addressed within 24 hours of data collection. All effort will be made to minimize missing data. There will be no imputation of missing data.

All data collected will be password protected and stored in a local server in each site. Each data collector will have a user name and a password and will have access to the next form to be filled. Completed forms will not be edited by data collectors. Local data manager and PIs will have access to complete data. Each participant will have a study identification number and all variables that would allow identification of subjects will be separated from the main dataset.

A central data repository will be created at the WHO. Sites will send cleaned data every month to WHO, and additional checks will be run and a list of queries will be sent to the sites for clarification. All data sent to WHO will not have any personal identifiers.

The data from this multi-center study will be accessible to all the participating research teams to jointly answer the study questions. After publication of the manuscripts reporting the results on primary and secondary outcomes, the data will be made publicly accessible.

Data analysis

The primary analysis will be executed by intention to treat. Even if the KMC is discontinued because of clinical conditions of the mother, the neonate will not be excluded. Effect size will be estimated with comparison of intervention and comparison group mortality risks. The two

primary outcomes are complementary, so adjustment for type I error is not needed. Results will be reported using CONSORT statement. A detailed analysis plan will be developed and published as part of the methods paper before the end of data collection.

Baseline characteristics will be presented by group to describe the study population and to check the success of randomization. Descriptors will be summarized as means and standard deviations for continuous variables; and frequencies and percentages for categorical variables. In case there are important differences in some of the baseline characteristics, results adjusted for these characteristics will be presented.

Effect sizes and their 95% confidence intervals will be calculated for the primary outcomes. Significance tests with 5% significance level will be performed and p values will be reported. If loss to follow up for primary outcomes is below 2.5% for mortality, we will calculate risk ratios and their confidence intervals. If loss to follow up for primary outcomes is greater than 2.5%, Hazards Ratios and their confidence intervals will be calculated. If important differences in baseline characteristics between intervention and control groups are identified, multiple logistic regression or Cox proportional hazards models will be used to adjust for confounding.

Subgroup analysis will be conducted for the two mortality outcomes by: (1) birth weight categories, 1.0 to <1.2, 1.2 to <1.5 and 1.5 to <1.8 kg, (2) gestational age at birth categories,<31, 31 to <34, 34 to <37 weeks, and (3) singleton or multiple births (4) small for gestational age or not (5) by mode of delivery i.e. normal vaginal delivery or cesarean section. Statistical tests of interaction will be used to interpret if the effect sizes in the categories are different or similar.

A secondary analysis stratified by compliance to Immediate KMC over 72 hours of age will be done. This analysis will report on efficacy of the intervention by average duration of skin-to-skin contact, classified as ≥20 hours/day; 10-19 hours/day; and <10 hours/day. In this secondary analysis, reverse causality may be an important issue because severely ill newborns may receive less or no skin-to-skin contact. To reduce the possibility of reverse causality, in this analysis we will exclude the babies who show signs of severe illness in the first 6 hours of life.

Study oversight

Steering Committee

The study Steering Committee will consist of all Principal Investigators from study sites, study consultants, BMGF representatives and WHO technical staff functioning as its secretariat. WHO will be responsible for organizing Steering Committee meetings prior to study implementation, 9-12 months into the study and at the end of the study. This committee will be responsible for designing and implementing the study in a harmonized way.

There are two Principal Investigators from each participating site. Study PIs have a role in the development of the research protocol, questionnaires, informed consent forms, manual of operations and the data management system. They will be responsible for all aspects of study implementation in their respective sites. They will be custodians of the data from their sites, with a commitment to public access to data after the study findings are published. The site

PIs are responsible for all patient related issues and are guarantors of data. They are expected to report periodically to WHO and to respond to requests in a timely manner.

WHO will coordinate the study, ensuring arrangements in place to support teams in any challenges being faced to implement this study. All trial activities will be coordinated and supported by WHO. Study progress will be monitored on a fortnightly basis through a brief report from each site followed by a teleconference. At these calls, progress of enrolment and follow up, and any challenges faced by the study team will be discussed. In addition to these operational reports, the sites will submit to WHO informal technical and financial reports every 6 months and detailed formal reports every year.

WHO technical staff will conduct monitoring visits to each site every year. There, a detailed structured review of study implementation at each visit will take place. Monitoring visits will have the dual function of identifying problems and supporting their solution in improving intervention delivery quality, data collection and monitoring.

Data and Safety Monitoring Board (DSMB)

A DSMB for the trial will be established by WHO before initiation of enrollment of participants. This group will be composed of five external, independent members with expertise in epidemiology, statistics, neonatology and social sciences. The members will be independent of the trials (e.g. they are not be involved with the trials in any other way). Each member of the DSMB will serve in his/her individual capacity. The DSMB will decide stopping rules for early benefit, harm or futility. The DSMB will be responsible for monitoring safety of trial participants, and will advise on continuation, modification, or termination of the trial.

The overall responsibilities and roles of the DSMB will be:

- to safeguard the interests of trial's participants, potential participants, investigators and sponsors;
- to assess the safety and early efficacy of the trial's intervention according to data available at a predefined schedule;
- to monitor the trial's overall conduct and quality, and protect its validity and credibility;
- make recommendations concerning continuation/termination of study or any other modification necessary based on the observed effects of the intervention.

On the basis of data management reports, site visits reports, and the statistical report, the DSMB will undertake interim review of the trial's progress by:

- assessing data quality, including completeness (thereby encouraging collection of high quality data)
- monitoring recruitment figures and missing data for outcomes
- monitoring compliance with the protocol by participants and investigators
- monitoring evidence for group differences in the main efficacy and safety outcome measures and thus recommending action when/whether the main trial question has been answered

- monitoring evidence for harm e.g. periodic review of mortality outcomes, and urgent review of each unexpected death. WHO technical unit will establish a special reporting system for immediate information about unexpected deaths.
- recommending whether the trial/s should continue to recruit (see section on decision-making)
- recommending any major changes to the protocol, where necessary (e.g. changes to the recruitment procedures, inclusion criteria, endpoints, data collection, etc.)
- advising on and/or endorsing any major protocol modifications suggested by investigators or sponsors (e.g. changes to the inclusion criteria, endpoints, data collection, etc.)
- monitoring planned sample size with regards to assumptions about the control arm outcome
- assessing the impact and relevance of any external evidence that becomes available
- monitoring compliance with previous DSMB recommendations

All DSMB members will review the protocol before agreeing to join the Board. If a potential DSMB member has major reservations about the trial/s they should report these to WHO and may decide not to accept the invitation to join. DSMB members should be independent and constructively critical of the ongoing trials, but also supportive of aims and methods of the trials.

The initial DSMB meeting will occur before the start of the trials. At this meeting, the DSMB will discuss and formulate the DSMB charter which includes triggers set for data review or analyses, definition of a quorum, format used in the reports and guidelines for monitoring the study. Guidelines should also address stopping the study for safety concerns and, where relevant, for efficacy based on plans specified in the protocol. At this meeting, the DSMB should also develop procedures for conducting business (e.g., voting rules, attendance, etc.).

A short competing interest/conflict of interest form should be completed and returned by the DSMB members. In the event that a person is unable to continue as a DSMB member, a new member (of similar expertise) will be appointed.

The Chair is expected to facilitate and summarize discussions. The DSMB statistician will provide independent statistical expertise, conduct per group interim analyses and to further guide the other DSMB members through the reports. DSMB members or their employers will not be paid. However, members will be reimbursed for any reasonable travel, accommodation or other costs (e.g. telephone) incurred.

The DSMB will meet at least once every 6 months, either in person or electronic. The DSMB and/or WHO may propose a meeting schedule or non-planned meetings according to the needs of the trial. The WHO technical unit will be responsible for the development of the statistical analysis plans (interim and final). The analysis plans will be formally reviewed and approved by the DSMB, with the approval documented in DSMB reports.

Two interim analyses are planned to enable decisions to stop the trial being made due early efficacy or safety concerns. These two interim analyses will be conducted when 33% and 67% of the required sample size has been enrolled. For early efficacy, a p-value of 0.001 will be used for recommending early stopping, according to the Haybittle-Peto rule. On the other hand, a p-value of 0.05 will be considered sufficient to stop the trial in case of harm.

Serious Adverse Events monitoring

Serious Adverse Event Definition: An adverse event is considered serious if it poses a threat to the patient's life or functioning. The US Food and Drug Administration (FDA) defines a serious adverse event (SAE) as any untoward medical occurrence that:

- Results in death,
- Is life-threatening (places the patient at risk of death), or
- Requires hospitalization or prolongs an existing hospitalization, or
- Causes persistent or significant disability or incapacity, or
- Is a birth defect, or
- Requires medical intervention to prevent one of the above outcomes.

This definition on its own is however not very useful if the research is being conducted on participants who are in a life threatening condition at the time of enrolment in the study. Babies born with a birth weight between 1.0 and 1.8 kg are at significantly higher risk of death and a range of severe morbidities. Many serious newborn conditions including death are pre-specified outcomes of the study. Thus, they are recorded as outcomes in study forms, rather than SAEs. The frequency of these outcomes will nonetheless be routinely reviewed by the DSMB.
However, if a death is considered to be unexpected, it will be reported on an urgent basis and reviewed by the DSMB on an individual basis.

Unexpected death: If there is death of an enrolled baby that would not be expected based on his/her condition, it will be reported within 24 hours of its occurrence to WHO. This will especially include any sudden unexplained infant death, as it could be potentially related to the intervention.

The investigator will be responsible for informing the relevant local authorities, IRB or committees, in accordance with their rules and standards.

Additional information relevant to an unexpected death such as hospital records, results from investigations, e.g. laboratory parameters, invasive procedures, scans and X-rays, and autopsy results can be faxed or scanned and e-mailed using the contact details in the section above. In any case this information must be supplied by the investigator upon request from WHO. On any copies provided, such details such as participant's name, address, and hospital ID number should be concealed and instead participant number should be provided.

Once a report of an unexpected death is received, the WHO team inform the trial DSMB within 24 hours of receiving the information. The DSMB will review these cases and make judgments regarding safety concerns and continuation of the study.

Technical Advisory Group (TAG)

The study TAG will advise WHO and the Principal Investigators on the implementation of the trial. The group will be composed by three to five experts in the field with clinical, public health and health systems background. It will also have the chair of the DSMB as its member. The TAG members will serve in their individual capacity.

The TAG will review the final research protocol for any major concerns prior to trial implementation. TAG members' terms of reference also includes review of manual of operations, study forms and consent forms and advise on practical issues in implementing the trial in the field. WHO will serve as secretariat to this group and organize two meetings, one before the study starts and one after one year of study. The TAG will review study progress periodically and advise on ways to improve the implementation of different aspects of the trial.

Time line

The first nine months of the study will be dedicated for preparation, the next two years for enrollment and data collection, and the final six months data analysis, interpretation and manuscript development. The activities in these phases are briefly described below:

A. Preparatory phase (9 months)

1) Finalization of study protocol, consent forms and questionnaires.
2) Obtaining ethical approvals from WHO-ERC and institutional ethics committees.
3) Contracts with the sites.
4) Development of standard operating procedures
5) Site preparedness: (i) Hiring and training of the study teams, (ii) customization of in hospital policies/clinical care protocol for successful conduct of the study, (iii) Set-up research facilities/infrastructure, identify or procure equipment and supplies required for the study, (iv) training and standardization, and (v) establishment of the data management system.
6) Formative research including pilot implementation of the intervention, and
7) Finalization of the implementation strategy.

B. Study implementation phase (24 months)

1) Pre-screening, consent, screening, post-birth consent and randomization 24 hours x 7days in the labor ward and operation theater.
2) Intervention delivery – in the delivery room or Operation Theater, and in the special care newborn unit. The KMC support research assistant will help the mother or the surrogate in providing skin-to-skin contact, and support the mother in breastfeeding.
3) Outcome measurement – data on primary and secondary outcomes collected on all enrolled children, in the hospital and at home visits.

C. Finalization phase (6 months)

1) Data cleaning.
2) Data analysis and manuscript preparation.
3) Dissemination of results
4) Synthesis of evidence for guidelines development.

Gantt chart showing activities and timelines

	1	2	3	4	5	6	7	8	9	10	#	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
A. Preparatory phase (9 months)																																							
Finalization of study protocol, consent forms, questionnaires and standard operating procedures	x	x	x																																				
Obtaining ethical approvals form WHO-ERC and institutional ethics committees.				x	x	x																																
Sub-contracts with sites							x	x	x																														
Site preparedness																																							
establishment of the investigator team				x																																		
involvement of the national and sub-national				x																																		
modification in hospital policies for successful conduct of the study					x																																	
preparation for care of enrolled mothers and					x																																	
study staff recruitment and training						x	x	x																														
establishment of the data management system						x	x	x																														
B. Study implementation phase (24 months)																																							
Screening, Enrollment, Delivery of the intervention, Outcome measurement									x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x								
C. Finalization phase (6 months)																																							
Completion of follow up and data cleaning																																	x	x					
Data analysis and manuscript preparation																																		x	x	x	x	x	x
Dissemination of results																																			x	x	x	x	x
Synthesis of evidence for guidelines development																																			x	x	x	x	x

Risks to the study and their mitigation

Political instability is a significant risk to the successful completion of the project. We have selected relatively stable countries and settings within countries (Ghana, India, Malawi, southern Nigeria and Tanzania).

Another risk to the project is not finding adequate number of eligible neonates to be recruited. We have reviewed the numbers of babies born at each site in 2015 and are confident that we will be able to recruit the required number of eligible babies within the planned two year enrolment period.

Finally, we may have lower than expected mortality in the control group during the study period, resulting in lower than optimal statistical power. We have taken a conservative estimate of mortality in the control group for sample size calculations. This rate will be monitored by the DSMB and sample size will be adjusted within 6-12 months of initiation of study implementation.

Amendment of Protocol

Changes to the protocol during the study will be documented as 'amendments'. All amendments, will be submitted to the relevant Ethics Committee for approval before implementation.

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ANNEX 1: Description of study sites, including experience with KMC

Ghana, Kumasi

KMC is being implemented in the study site in Ghana (Komfo Anokye Teaching Hospital) since 2007. The babies are provided intermittent KMC in the special care baby unit which has the infrastructure to provide comfort for the mothers providing KMC. The staff has acquired a lot of hands-on experience in providing KMC and they have a lactation counsellor in place to provide breastfeeding counselling and support to the mothers.

Komfo Anokye Teaching Hospital is the tertiary referral hospital for regions in middle and northern sector of Ghana. The Directorate of Child Health (DCH) of the Kwame Nkrumah University of Science and Technology's (KNUST) School of Medical Sciences at the Komfo Anokye Teaching Hospital (KATH) is supposed to coordinate the implementation of this study. Directorate has the neonatology unit (Mother & Baby Unit, MBU) and works very closely with the Obstetrics and Gynecology unit of the hospital. The hospital has 1200 beds and serves a population of 2 million. DCH sees over 20,000 outpatients yearly with over 11,000 inpatient admissions of all babies up to the 2nd month after birth. Preliminary data suggests 21 % intra hospital mortality among 1.0 to 1.8 kg babies. Data on neonatal mortality after hospital discharge are not available.

The MBU at KATH has a total bed capacity of 80 and is sub-divided into an Emergency Unit, a Low birth weight Unit, two Stable baby Units, and a new KMC ward. The MBU admits, on average, 15 babies per day and consequently 450 every month. There are four senior specialist pediatricians who are experienced in newborn care, 3 Pediatricians, 5 Pediatric Residents, 11 House officers, 44 nurses including specialist neonatal nurses and other support staff (2 critical care nurses and 3 specialist neonatal nurses in training). The MBU is directly linked to parts of the Obstetrics and the Gynecology Unit (O&G) of the hospital. The labor ward is located on a floor below MBU. The O&G is a 180 bed-capacity unit with a labor ward having 10 delivery beds. The O&G has a theatre for obstetric operations including caesarean sections.

India, New Delhi

KMC is being implemented in the study site in India (Safdarjung hospital) since a few years now. The babies are provided intermittent KMC inside NICU once they are stable and when the baby is on full cup feeds / breast feeds, the baby is shifted with mother to KMC ward and KMC is continued there. On an average KMC is done for 6 to 8 hours/day by the mothers in KMC ward and the staff has experience in providing KMC support and breast feeding counselling and support to the mothers.

Safdarjung hospital is a 1531 bedded tertiary care hospital with attached Vardhman Mahavir Medical College catering to a large population of Delhi and serves as a referral center for a significant part of north India. It has facilities for all modern and comprehensive diagnostic services. The Obstetric division of Obstetrics and Gynecology department comprised of 227 beds and has 6 units. All mothers are accompanied by a family relative from antenatal to postnatal period as birth companion. Approximately 20,000-22,000 deliveries occur annually in this hospital and 20-25% of these are delivered by caesarean section. The neonatal division of pediatric department provides comprehensive newborn care which includes preventive and curative services, education and training to paramedics, nursing personnel and resident doctors. The neonatal division has two units and caters to 18 - 20% of births requiring nursery admission. Each NICU is 25 bedded with neonatal occupancy rate of 115 to 120%.

Babies delivered in labor room or operation theatre requiring admission, are immediately transferred in transport incubators to NICU as per admission criteria (babies < 1800 gm, preterm <35 weeks for assisted feeding, moderate to severe respiratory distress or birth asphyxia, neonatal jaundice and major congenital malformation). In last 6 months, 868 babies weighing 1.0 kg to 1.8 kg were admitted in neonatal intensive care unit. Of these 142 babies (16.3%) died in the hospital. About 8% of those discharged alive died before 6 weeks of age.

Malawi, Blantyre

KMC is being implemented in the study site in Malawi (Blantyre- Queen Elizabeth Central Hospital-QECH) since November 2003. Babies less than 1800g are admitted to the KMC ward once stable. In the KMC ward mothers, aunts and grandmothers care for babies in skin to skin position, supervised and supported by trained nurse midwives. Mothers are also supported in providing breast feeding to their babies. Most staff have had some orientation on KMC and BFHI (breast feeding hospital initiative). QECH even runs outpatient KMC follow up clinics once every week and these are done by midwives, Clinical Officers and medical officers.

Queen Elizabeth Central Hospital (QECH), a government facility, is both a tertiary government referral unit for the Southern region and a district hospital for Blantyre city and its surrounding health centers. In QECH, there are nearly 14,000 deliveries per year (HMIS), many of which are designated high risk. The nursery offers level-2 neonatal care. A Kangaroo Care inpatient ward was opened in November 2003. It was recently expanded and now has 35 beds and is run by pediatricians; clinical officers nurse midwives and patient attendants (non-specialist, non-clinical staff with high-school qualifications and on-the-job training). Mothers carry out all infant care under the support and supervision of the midwives and patient attendants. QECH runs outpatient KMC follow up clinics once every week and these are done by midwives and medical officers. The QECH provides health care for 800,000 to 1000,000 inhabitants of the catchment area.

In QECH the number of 14,000 births occurs every year. The obstetric unit has 80 beds and a caesarian section rate of 15%. The neonatal unit has 65 neonatal beds split in to KMC unit (35 beds) and High level care unit (level 2 – 15 beds) and the remaining are level 1 care (after care unit). Preliminary data suggests 23 % intra hospital mortality among 1.0 to 1.8 kg babies. There is no estimation of neonatal mortality after hospital discharge.

Nigeria, Ile Ife

KMC is being implemented in the study site in Nigeria (Ile-Ife hospital) since the past 2 years. The PI and the head nurse went to learn how to establish a KMC unit to Malawi, and established such a unit 2 years ago. The babies are provided intermittent KMC inside NICU once they are stable and when the baby is on full cup feeds / breast feeds, the baby is shifted with mother to KMC ward and KMC is continued there. On an average KMC is done for about 8 hours/day by the mothers in KMC ward and the staff has experience in providing KMC support and breast feeding counselling and support to the mothers. The hospital is a Baby Friendly Hospital with midwives experienced in counselling on breast feeding and well above 90% of the mothers routinely breastfeed.

The Obafemi Awolowo University Teaching Hospitals Complex, (OAUTHC) is a tertiary health facility and is a conglomerate of 6 hospital units. Of the six units the Wesley Guild Hospital (WGH) and Ife Hospital Unit (IHU) provide neonatal care. The IHU is proposed for implementing this study. IHU serves a population of over 30 million with 4 million from Osun state where it is domicile. The IHU has a well-equipped Obstetric section that renders basic and higher level obstetric care to pregnant women. The Unit provides antenatal, intrapartum and postnatal obstetric services, as well as accepts complicated referrals from other primary and secondary health facilities. The Obstetric unit has 13

consultant Obstetricians, and 34 Resident doctors at various levels of specialist training. In IHU, there are 65 beds and 79 trained Nurses and Midwives in the obstetric wards, rendering dedicated care to the patients. The IHU conducts an average of 300 deliveries per month. The Caesarean Section rate is around 40% on the average. Companionship in labor is provided by the Nurses/Midwives, although women in labor are allowed to come with their relatives, who will wait at the labor ward lounge, where they are given serial updates on the progress of events.

The neonatal unit of the IHU is 25 bedded. Currently the neonatal ward is manned by two consultant neonatologists, four resident doctors, four house officers and 18 nurses with 24 hours coverage. Average cot/incubator occupancy rate is 90%. Attached to the neonatal ward is a newly constructed 10 bedded KMC ward where stable babies are transferred with their mothers for continuous KMC. A new maternity unit is being constructed including neonatal unit with 50 neonatal beds to be in use before December 2016. This new unit offers appropriated infrastructure to promote immediate KMC for unstable neonates. Currently, the total intra hospital mortality among 1.0-1.8 kg is 48.2%.

Tanzania, Dar es Salaam

KMC is being implemented in the study site in Tanzania (Muhimbili Hospital) since August 2012 and is provided to the preterm babies who are stable, as per the present WHO guidelines. More than half of the nurses in the newborn unit have received training in Kangaroo mother care and essential newborn care, which includes breastfeeding counselling , positioning and attachment. Furthermore this hospital is a baby friendly hospital, so exclusive breastfeeding is promoted as the best infant feeding option and culturally also most of the mothers breastfeed their children unless contraindicated.

Muhimbili National Hospital (MNH) is both a tertiary referral and teaching hospital for Muhimbili University of Health and Allied Sciences, Dar es Salaam. The hospital receives referrals (including obstetrics and newborn patients) mostly from Regional Referral Municipal hospitals in Dar es Salaam and few from other regions of Tanzania. Obstetric care and neonatal unit are offered in one building which gives a combined access to care of mother and baby. The care is provided by 29 obstetricians, three general doctors (registrars) and 45 nurses. The labor ward has 20 beds and the high dependent ward has 21 beds, both located on the first floor of the main maternity block. The caesarean rate at MNH is around 40% and 20 to 40 deliveries occur in 24 hours, with 25% of them weighing between 1-1.8 kg.

The neonatal unit has approximately 140 baby cots. Previously restricted to only left wing (Preterm high and lower care), but recently expanded to the right wing (Well term babies). The KMC ward recently moved to the maternity 2 building, total number of beds 16, (will increase to 25 once one room becomes available). All neonatal care is provided by 10 Pediatricians, 1 registrar, 38 Nurses (27 in left and right wings plus 11 in KMC) and 17 nurse assistants (12 in left and right wings plus 5 in KMC ward). MNH neonatal unit received in the past 6 months a total of 940 preterm babies (born 1kg -1.8kg) including 456 out born (referred) babies and 484 in born babies. During this period the total intra hospital mortality among 1.0 to 1.8 kg for inborn babies was 22%. No data on mortality at 28 days was provided.

ANNEX 2: List of study questionnaires

Name of the form	What is the purpose?	For whom?	When?	Where?	By Whom?
PRE SCREENING FORM	Identify mothers at high risk of delivering a low birth weight baby	All mothers admitted for childbirth	At the time of admission for childbirth	Admission room, Labour ward or ANC ward	Screening & Enrolment RA
INFORMED CONSENT FORM	Provide information about study, , give opportunity to ask questions, check understanding, and take consent for participation	Mothers with a high risk of delivering a LBW baby	At the time of admission for childbirth	Admission room, Labour ward or ANC ward	Screening and Enrolment RA
SCREENING FORM	Record pregnancy, childbirth and newborn related information and assess eligibility for enrolment	All births in the hospital	As soon as possible after childbirth	Delivery room, Labour ward or Operation Theatre	Screening and Enrolment RA
POST-BIRTH INFORMED CONSENT FORM	Inform about the study, give opportunity to ask questions, check understanding, and take consent for participation	Mothers of eligible babies who have not provided consent before birth Surrogates if mother-baby allocated to intervention group	After confirmation of eligibility	Delivery room, Labour ward or Operation Theatre	Screening and Enrolment RA
ENROLMENT FORM	Enrol and assign mother-baby to either intervention or control group; document transfer and admission to neonatal unit	All mothers who have given consent	After confirming consent	Delivery room, Labour ward or Operation Theatre	Screening and Enrolment RA
BASELINE FORM	Collect mother, family and environment related information; document contact details	All enrolled mother-baby pairs	Anytime during admission in neonatal unit	Neonatal unit	Outcome measurement RA (hospital)
FOLLOW UP FORM	Document vital status of the baby, time to stabilization, assess for infection, record feeding information, document health care provided and duration of KMC	All enrolled babies	Every 12 hours until discharge	Neonatal unit or KMC ward	Outcome measurement RA (hospital)
DISCHARGE FORM	Document date and time of discharge, maternal/family satisfaction with health care experience, mother's address and other contact details	All enrolled babies who are discharged from hospital	Around time of discharge	Hospital	Outcome measurement RA (hospital)

29-DAY FORM	Assess vital status at the end of the neonatal period, exclusive breastfeeding and maternal postpartum depression	All enrolled babies	On day 29 after birth	Hospital/ home	Outcome measurement RA (hospital or home)
Non enrolled babies' follow up Form	Vital status of non-enrolled babies 72h after birth	All 1.0-1.8 kg babies who are not enrolled	72 hours after birth	Hospital/ Home	Outcome measurement RA (hospital or home)
Neonatal death form	Capture information about cause of death in the hospital	Neonatal death in hospital	Any time after a participant dies in the hospital	Hospital	Outcome measurement RA (hospital)
Verbal autopsy form	Capture information about cause of death in the in the community	Neonatal death after discharge	Any time after a participant dies at home	Home	Outcome measurement RA (home)

ANNEX 3: Additional site-specific information required by WHO-ERC

Site-specific information – India, Safdarjung Hospital
(Annexure to Master Protocol version 3.0, 30 September 2017)

Introduction: The Immediate KMC study master protocol has already been approved by WHO ERC. This document is an Annexure to the immediate iKMC study master protocol, and provides additional information from India site i.e. Safdarjung Hospital. We confirm that the study in India site will fully conformed to the master protocol.

Additional Information:

1. The India site of this multi-centre study – Safdarjung Hospital – will adhere to all elements of the master protocol.

2. **Study area:** Study will take place in Safdarjang Hospital situated in capital of India which is a developing country. Safdarjung Hospital is a tertiary care referral centre for many hospitals in Delhi, and surrounding National Capital Region. It mainly caters to people of lower middle and middle socio economic strata, with an education background that varies from illiterate to graduate mothers

3. **Description of site:** The study will be conducted in Paediatrics and Obst & Gynae Department, Safdarjung Hospital, New Delhi. Among the deliveries, there is a high proportion of preterm and small for gestational age babies, because women with complications are frequently referred to this hospital from smaller health facilities.

   In this hospital, babies with birth weight <1.8 kg are routinely provided care in NICU. Care provided in NICU includes warmth, breast-milk feeding, and if required, intravenous fluids, parenteral antibiotics, oxygen, and continuous positive airway pressure, surfactant therapy and mechanical ventilation. KMC is practiced in this hospital after achieving stabilization, usually after 3-7 days of age. Review of records from the hospital for the past year shows that the number of infants born with birth weight 1.0 to <1.8 kg, varied between140 to 180 per month.

   In addition to the Principal Investigator (Prof Harish Chellani, Paediatrics) and co-investigators from Obstetrics (Prof Pratima Mittal, Dr Anand and Dr Jyotsna Suri) and Paediatrics (Dr Sugandha Arya, Dr Nidhi Chopra) Departments, a number of research staff will be employed specifically for the project. An overall project coordinator will be responsible for overseeing day to day activities of all teams. A total of 8 research nurses will work in shifts so that two of them are always available for screening and enrolment. Six research nurses and 10 KMC support workers will be employed to support women

enrolled in the study to deliver the intervention. In addition, five field workers will collect outcome data.

4. **Description of process of identification of potential participants:** During antenatal visit in Gynae Obst OPD the high risk mothers (like with high BP, anaemia, < 18 years age) will be given written information (printed sheet, Hindi version attached) about the study, and the attending doctor will brief them about the study. Dr Jyotsna Suri, a co-investigator in the study from the Department of Obstetrics and Gynecology will be the focal person who women can ask questions or get further information about the study.

5. **Complete description of consent (and assent process):** The process will be as exactly described in the master protocol.

   All pregnant women admitted in hospital for childbirth in labor, or before caesarean section, will be screened for the risk of delivering a low birth weight baby in Gynae Receiving room (GRR). If a mother is likely to deliver a low birth weight baby, Research Nurse 1 will provide all the information about the study and seek her consent for participating in the study. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. After birth of the baby, if all the inclusion criteria are met and none of the exclusion criteria are present, the consent of the mother will be verbally confirmed in the labor room /Operation Theatre by the Research Nurse 2.

   In situations where a baby is born unexpectedly very small, the Research Nurse 2 has no alternative but to obtain consent from mothers just after delivery. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. However, these mothers will be given the opportunity to decide about continued participation in the trial 24 hours after birth. Research Nurse 2 will follow the mother.

   Mothers who are minors will be eligible for enrolment in this study if they are at least 15 years of age. Assent from the mother will be obtained before recruitment but the consent form will be signed by the minor mother's guardian (parent).

   If a woman is illiterate, an impartial witness will be present during the entire informed consent reading and discussion. The impartial witness will also sign and date the consent form, along with the individual who performed the informed consent discussion. All mothers considered to be at risk of delivering a small baby will be provided information about the study, and asked for consent for participation in the study in case they deliver a small baby who meets study eligibility criteria. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. The mothers will be asked to confirm their consent for participation in the study verbally within the first two hours after birth.

6. **Data Management:**
   a. The data management will be undertaken by CDSA & Safdarjung Hospital jointly. PI, Safdarjung Hospital & CDSA will oversee the process.

b. The data collected at the site will be reviewed by PIs, Co-PIs and authorized designated staffs of Safdarjung Hospital as well as CDSA QM team. A list of authorised persons who can access the data and their level of access rights details will be shared with WHO.
c. The data management will be as per the data management plan received from WHO.
d. CDSA & SJH will be jointly responsible for storage of the data at clinical site/ CDSA server (as per WHO directions and agreement).
e. Future Use & Destruction of the data will be done as per WHO / sponsor guidelines.
f. Routine Precautions to Protect Data Confidentiality will be taken care.
   i. The subject research identification codes will be used
   ii. Files containing electronic data will be password-protected and encrypted (at least when data are transferred or transported).
   iii. Research data/specimens will be stored securely in locked cabinets or rooms.
   iv. Electronic data will be stored in password-protected computers or files.
   v. Consent and authorization forms will be stored securely in locked cabinets or rooms, separately from the research data.
   vi. Research staff will be trained on the WHO ERC-approved SOP for managing and storing research data.

7. **Data Analysis:** The analysis will be done jointly in accordance with master protocol.

8. **Sample Size:** The sample size for comparison of two proportions (21.0% compared with 16.8%) is 2080 per group, thus a total of 4200 neonates will be required to be enrolled in all sites. Based on the number of neonates born in the selected hospitals, and assuming that we will be able to enroll about half of these births, enrolment can be completed in about two years.

COUNTRY/SITE	**Eligible 1.0-1.8kg infants**	**Expected enrolment per month**	**Expected enrolment in 2 years**
Ghana	50	25	600
India	140	70	1680
Malawi	50	25	600
Nigeria	30	15	360
Tanzania	80	40	960
Total	350	175	4200

9. **Dissemination Strategy**
   a. The results of the study will be disseminated to all the health workers in SJH through a meeting.
   b. Study participants will be informed about the results through a letter explainin the results in simple lay person language.
   c. A national results dissemination meeting will be held within 3 months of completion of data analysis, which will be attended by relevant Ministry of Health officials at both the central and state level, as well as professional associations.

d. The study outcomes will be reported at specific intervals, as agreed and approved by WHO. It may be published in peer-reviewed journals site specific and also with the multi country data.

10. **Additional ethical considerations:** As a clinical site investigators, India team do not foresee any additional ethical considerations and will ensure compliance with the protocol and project requirements outlined by WHO/ Sponsor. However, we will also abide by the applicable local regulations / hospital policies and standard of care for the management of the participants enrolled in this study.

11. **Translated consent forms (Hindi language) are attached**

12. **Local Ethical Approval is attached.**

13. **Budget of the India site:**

Year 1: US$ 279,507
Year 2: US$ 271,142
Year 3: US$ 63,505

14. **The CVs of the investigators have been submitted with the Master Protocol.**

Site-Specific Information for Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Nigeria.

(Annexure to Master Protocol version 3.0, 30 September 2017)

Introduction: The Immediate KMC study master protocol has already been approved by the WHO ERC. This document is an Annexure to the Immediate KMC (IKMC) study master protocol, and provides additional information from the Obafemi Awolowo University Teaching Hospital Complex (OAUTHC), Ile-Ife, Nigeria site. We confirm that the study site in Nigeria will fully conform to the master protocol.

Additional Information:

1. The OAUTHC, which is the Nigeria site of this multi-centre study, will adhere to all elements of the master protocol.

2. **Study area:** The study will take place in the Ife Hospital Unit of the OAUTHC. The hospital is situated in Ile-Ife which is about 250km to Lagos the commercial nerve of Nigeria, which is a developing country. The OAUTHC is a tertiary care referral centre for many hospitals in five states (Osun, Oyo, Ondo, Ekiti and Ogun states) in the southwest of Nigeria. It caters for people of all socioeconomic class although majority are from the lower socio-economic class.

3. **Description of site:** The study will be conducted in the Neonatal unit and the maternity section of the IHU of the OAUTHC, Ile-Ife, Nigeria. Among the deliveries, there is a high proportion of preterm and small for gestational age babies, because women with complications are frequently referred to this hospital from Primary and Secondary Health facilities in both Public and Private sectors.
   In this hospital, babies with birth weight <1.8 kg are routinely provided care in NICU. Care provided in NICU includes warmth, breast-milk feeding, and if required, intravenous fluids, parenteral antibiotics, oxygen, and improvised continuous positive airway pressure. Occasionally surfactant therapy is available for use. KMC is practiced in this hospital after achieving stabilization, usually after the first week of life. Published data from the hospital shows that 17% of all newborns in the hospital are low birth weight. Review of records from the hospital for the past year shows that the number of infants born with birth weight 1.0 to <1.8 kg, is an average of 30 per month.

   In addition to the Principal Investigator (Prof Ebunoluwa Aderonke Adejuyigbe, Paediatrics) and co-investigators from Obstetrics (Professors Oluwafemi Kuti, Adeyemi Babalola) and Paediatrics (Dr Henry Anyabolu, Dr Bankole Peter Kuti) Departments, a number of research staff will be employed specifically for the project. An overall project coordinator will be responsible for overseeing day to day activities of all teams. A total of 19 research assistants will be employed to work in shifts; there will be one nurse available every time of the day for screening and enrolment. There will be a study medical doctor covering the labour ward and labour ward theatre at all times and also medical doctors will cover the neonatal unit on a shift basis. Three KMC support staff will

be employed to provide support for women in the study ad six independent outcome assessors who will be study nurses.

4. **Description of process of identification of potential participants:** During antenatal visit in the Obstetric unit of the Department of Obstetrics, Gynaecology and Perinatology the high risk mothers (such as those with high BP, anaemia, short stature or aged less than 18 years) will be given written information (printed sheet, Yoruba translation version attached) about the study, and the attending doctor will brief them about the study. Professors Kuti and Babalola who are co-investigators in the study from the Department of Obstetrics and Gynecology will be the focal persons who women can ask questions or get further information about the study.

5. **Complete description of consent (and assent process):** The process will be as exactly described in the master protocol.

   All pregnant women admitted in hospital for childbirth in labor, or before caesarean section, will be screened for the risk of delivering a low birth weight baby in labour ward admission room. If a mother is likely to deliver a low birth weight baby, the screening Research Nurse will provide all the information about the study and seek her consent for participating in the study. Before taking consent, the treating physician or midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. After birth of the baby, if all the inclusion criteria are met and none of the exclusion criteria are present, the consent of the mother will be verbally confirmed in the labor room /Operation Theatre by the Enrolment Nurse.

   In situations where a baby is born unexpectedly very small, the Enrolment Nurse has no alternative but to obtain consent from mothers just after delivery. Before taking consent, the treating physician or midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. However, these mothers will be given the opportunity to decide about continued participation in the trial 24 hours after birth. The Enrolment Nurse will follow-up the mother for this consent.

   Mothers who are minors will be eligible for enrolment in this study if they are at least 15 years of age. Assent from the mother will be obtained before recruitment but the consent form will be signed by the minor mother's guardian (parent).

   If a woman is illiterate, an impartial witness will be present during the entire informed consent reading and discussion. The impartial witness will also sign and date the consent form, along with the Research Assistant who performed the informed consent discussion. All mothers considered to be at risk of delivering a small baby will be provided information about the study, and asked for consent for participation in the study in case they deliver a small baby who meets study eligibility criteria. Before taking consent, the treating physician or midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. The mothers will be asked to confirm their consent for participation in the study verbally within the first two hours after birth.

6. **Data Management:**
   a. The data management will be undertaken by the Investigating team which includes an Epidemiologist. The Principal Investigator will oversee the process.

b. The data collected at the site will be reviewed by the data Manager, PIs and other investigators. A list of authorized persons who can access the data and their level of access rights details will be shared with WHO.
c. The data management will be as per the data management plan received from WHO.
d. The PI and data management team will be jointly responsible for storage of the data at the Research Office.
e. Future Use & Destruction of the data will be done as per WHO guidelines.
f. Routine Precautions to Protect Data Confidentiality will be taken care.
   i. The subject research identification codes will be used
   ii. Files containing electronic data will be password-protected and encrypted (at least when data are transferred or transported).
   iii. Research data will be stored securely in locked cabinets in rooms marked 'Out of Bounds'.
   iv. Electronic data will be stored in password-protected computers or files.
   v. Consent and authorization forms will be stored securely in locked cabinets or rooms, separately from the research data.
   vi. Research staff will be trained on the WHO ERC-approved SOP for managing and storing research data.

7. **Data Analysis:** The analysis will be done jointly in accordance with master protocol.

8. **Sample Size:** The sample size for comparison of two proportions (21.0% compared with 16.8%) is 2080 per group, thus a total of 4200 neonates will be required to be enrolled in all sites. Based on the number of neonates born in the selected hospitals, and assuming that we will be able to enroll about half of these births, enrolment can be completed in about two years.

COUNTRY/SITE	Eligible 1.0-1.8kg infants	Expected enrolment per month	Expected enrolment in 2 years
Ghana	50	25	600
India	140	70	1680
Malawi	50	25	600
Nigeria	30	15	360
Tanzania	80	40	960
Total	350	175	4200

9. **Dissemination Strategy**
   a. The results of the study will be disseminated to all the health workers in OAUTHC by sharing during the Hospital Grand Round meeting.
   b. Study participants will be informed about the results through a letter explaining the results in simple lay person language.
   c. A national results dissemination meeting will be held within 3 months of completion of data analysis, which will be attended by relevant Ministry of Health officials at the state and the national level, as well as professional associations.

d. The study outcomes will be reported at specific intervals, as agreed and approved by WHO. Site specific findings and multi-country data will be published in peer-reviewed journals.

10. **Additional ethical considerations:** The Nigeria team do not foresee any additional ethical considerations and will ensure compliance with the protocol and project requirements outlined by WHO and the Sponsor. We will also abide by the applicable local regulations and hospital policies and standard of care for the management of the participants enrolled in this study.

11. **Translated consent forms are attached**

12. **Local Ethical Approval is attached.**

13. **Budget of the site:**

Year 1: US$ 337,602
Year 2: US$ 305,080
Year 3: US$ 166,012

14. **The CVs of the investigators have been submitted with the Master Protocol.**

Site-specific information Tanzania, Muhimbili National Hospital
(Annexure to Master Protocol version 3.0, 30 September 2017)

Introduction

Muhimbili National Hospital (MNH) is both a tertiary referral and teaching hospital for Muhimbili University of Health and Allied Sciences, Dar es Salaam. The hospital receives referrals (including obstetrics and newborn patients) mostly from Regional Referral Municipal hospitals in Dar es Salaam and few from other regions of Tanzania. On average 10,000 deliveries occur annually, and 20 to 40 deliveries occur in 24 hours, with 25% of them weighing between 1-1.8 kg.

Additional Information

1. Muhimbili National Hospital, in Tanzania has been selected as part of a multi-country randomised clinical trial site sponsored by the WHO on: "***Safety and efficacy of Immediate Kangaroo MotherCare amongst preterm and low birth weight neonates weighing between 1.0kg to <1.8kg "***. Therefore, in the implementation of the study, MNH will adhere to all the aspects of the study implementation as per the master protocol.

2. Study Area

Study will take place in Muhimbili National Hospital (MNH), located in Dar es Salaam, the business capital of Tanzania, which is an urban and developing city with an estimated population of about 5.78 million inhabitants.MNH is a tertiary care hospital, research center and University teaching hospital. It also serves as a second level referral hospital, which receives patients from the three regional referral hospitals in Ilala, Temeke and Kinondoni municipalities. As a national referral center, MNH also receives patients from the other 30 regions in the country and has a 1500 bed capacity, attending to about 1000 to 1200 out-patients per day and admitting up to 1000 to 1200 patients per week. MNH has eight major medical services departments including: Emergency Medicine, Internal Medicine, Surgery and Surgical Specialties, Obstetrics and Gynaecology, Psychiatry, Orthopaedics and Trauma Unit, Cardiac Intervention Centre and the Department of Paediatric and Child health.

3. Description of site

The study will be conducted in the neonatal unit located on the second floor of the main maternity building. It has approximately 140 baby cots. The Kangaroo mother care (KMC) ward for stable babies is located in the maternity 2 building and has a total number of 30 beds. The unit receives premature babies weighing from 750 grams, transitioning from the neonatal unit. For preterm babies who have lost their mothers, family members are requested to bring a close relative that can offer KMC and they usually bring a grandmother, an aunt or a sister. Similarly for a mother with more than 2 babies i.e. triplets are also requested to identify and bring a family member who can assist to offer KMC to the third baby. The MNH neonatal unit received a total of 940 preterm babies (born 1kg -1.8kg) including 456 out born (referred) babies and 484 in born babies between June to December 2015

In the neonatal unit as well as stable KMC unit the routine care is provided by 10 Pediatricians, 1 registrar, 38 Nurses (27 in left and right wings plus 11 in separate KMC ward) and 17 nurse assistants (12 in left and right wings plus 5 in KMC ward) responsible for patient care. The study

PI at the MNH site is Dr Augustine Massawe (consultant neonatologist) and there are 3 pediatricians who saves as study co- PIs (Dr Helga Naburi, Evelyne Assenga and Robert Moshiro) other co investigators include Prof. Karim Manji (neonatologist), Dr Matilda Ngarina (obstetrician), Dr Mary Charles (Paediatrician & Head of Department), Dr Edna Majaliwa (Paediatrician & Head of newborn unit), Dr Martha Mkonyi (Paediatrician) and Sr. Cleopatra Calist (KMC Nurse).

We currently don't have names for the full time research staff. We have potential candidates and we are in a process of filling up 33 slots for research specific staffs including: 5 pre-screening team members, 6 enrolment team members, 6 outcome assessors, 8 KMC supporters, 2 Data clerks, 1 Data Manager, 3 follow up team members, 2 registrars 1 project accountant, and 1 study coordinator.

4. Description of process of identification of potential participants

Pregnant women attending antenatal care clinics in the participating hospitals will be given a printed sheet providing information about the trial if they are found to have a risk factor for having a low birth weight baby.This will be done face to face whereby high-risk pregnant women will be informed about the trial at antenatal care visits to MNH, or in the obstetric wards for women who have risk factors such as PPROM. The information will be conveyed to the participants by both the attending healthcare workers, doctors and nurses and by the dedicated research staff. There shall be no advertisement for recruiting of participants.However, the process of pre-screening and pre-consent will occur at the time the mother is admitted to the hospital for childbirth by trained research assistants designated as the prescreening and consenting officer

5. Complete description of consent (assent process)

All pregnant women admitted in hospital for childbirth in labor or before caesarean section will be screened for the risk of delivering a low birth weight baby. If a mother is likely to deliver a low birth weight baby, a research assistant will provide all the information **a**bout the study and seek her consent for participating in the study. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. After birth of the baby, if all the inclusion criteria are met and none of the exclusion criteria are present, the consent of the mother will be verbally confirmed within two hours after birth before randomization is done.

In situations where a baby is born unexpectedly very small, the research team has no alternative but to obtain consent from mothers just after delivery. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. Mothers who may have to give consent after delivery will again have verbal confirmation of their consent sought within 24 hours of enrolment into the study.

Mothers who are minors will be eligible for enrolment in this study if they are at least 15years of age. Assent from the mother will be obtained before recruitment but the consent form will be signed by the minor mother's guardian (husband or parent).

In the event that an expectant woman is illiterate, an impartial witness will be present during the entire informed consent reading and discussion. The impartial witness will also sign and

date the consent form, along with the individual who performed the informed consent discussion.

6. Data management

A standardized database for the study will be created using a standard data platform such as RedCap. All data collected will be password protected and stored in a local server in each site. At Muhimbili site each data collector will sign the data forms when handed to the data entry clerks. Data entry clerks will be hired for the purpose of the study and they will be responsible for entering the research data from the completed forms to the database, which will be automatically uploaded to the MUHAS data server. Local data manager and PIs will have access to the server and completed datasets for quality checks and will sign off before the WHO can review the data.

Data stored at MUHAS research office from this clinical trial will be retained for a minimum of 5 years duration from the date the study is closed. A formal request to then destroy the records will be completed as per the MUHAS standard procedure for the destruction of classified university records.

a. The data collected at the site will be reviewed by PIs, Co-PIs and authorized designated staff of MNH. A list of authorised persons who can access the data and their level of access rights details will be shared with WHO.
b. The data management will be as per the data management plan received from WHO.
c. Future Use & Destruction of the data will be done as per WHO / sponsor guidelines.
d. Routine Precautions to Protect Data Confidentiality will be taken care of.
    i. The subject research identification codes will be used
    ii. Files containing electronic data will be password-protected and encrypted (at least when data are transferred or transported).
    iii. Research data/specimens will be stored securely in locked cabinets or rooms.
    iv. Electronic data will be stored in password-protected computers or files.
    v. Consent and authorization forms will be stored securely in locked cabinets or rooms, separately from the research data.
    vi. Research staff will be trained on the WHO ERC-approved SOP for managing and storing research data.

7. Data analysis

The analysis will be done jointly in accordance with master protocol.

8. Sample size

The sample size for comparison of two proportions (21.0% compared with 16.8%) is 2080 per group, thus a total of 4200 neonates will be required to be enrolled. Based on the number of neonates born in the selected hospitals, and assuming that we will be able to enroll about half of these births, enrolment can be completed in about two years. Tanzania will contribute a total of 960 neonates to the sample size.

COUNTRY/SITE	**Eligible 1.0-1.8kg infants**	**Expected enrolment per month**	**Expected enrolment in 2 years**
Ghana	50	25	600

India	140	70	1680
Malawi	50	25	600
Nigeria	30	15	360
Tanzania	80	40	960
Total	350	175	4200

9. Dissemination strategy

Findings will be disseminated locally to the Muhimbili National Hospitaladministration, the MUHAS scientific committee, the National Institute of Medical Research of Tanzania and the Ministry of Health, Community Development, Gender, Elderly and Children. This will be done through formal meetings whereby the final report will be presented and copies of the report distributed. Data will also be presented in various international conferences and publications will be done in peer-reviewed journals.

10. Additional ethical consideration

There are no additional ethical considerations required for the Tanzania site different from what is included in the master protocol and Tanzania will adhere to ethical guidelines and GCP requirements stipulated in the master protocol. Tanzania will also abide to the Muhimbili University of Health and Allied Science, Muhimbili National Hospital and the National Institute of Medical Research local ethical guidelines

11. Translated consent forms attached

12. Local Ethical Approvals attached

13. Budget of the site attached
Year 1 $ 297,853
Year 2 $ 257,767
Year 3 $ 144,370

14. The CVs of the investigators have been submitted with the Master Protocol

Site-specific information – Ghana, Komfo Anokye Teaching Hospital
(Annexure to Master Protocol version 3.0, 30 September 2017)

Introduction: The Immediate KMC study master protocol has already been approved by the WHO ERC. This document is an Annexure to the immediate iKMC study master protocol, and provides additional information from the Ghana site i.e. Komfo Anokye Teaching Hospital (KATH). We confirm that the study in Ghana site will fully conform to the master protocol.

Additional Information:

15. The Ghana site of this multi-centre study – Komfo Anokye Teaching Hospital (KATH) – will adhere to all elements of the master protocol.

16. **Study area:** The study will take place in the Komfo Anokye Teaching Hospital situated in Kumasi, the second largest city in Ghana which is a lower middle-income country in West Africa. Komfo Anokye Teaching Hospital is a tertiary care referral centre with 1200 beds and serves a population of about 2 million. It serves the regions in the middle and northern sector of Ghana and the Department of Child Health (DCH) sees over 20,000 outpatients yearly with over 11,000 inpatient admissions of all babies up to the 2nd month after birth. It caters to all manner of patients who attend the hospital many of whom are registered on the National Health Insurance Service (NHIS).

17. **Description of site:** The Ghana component of the study will take place in the new Mother Baby Unit of the KAH which has a total bed capacity of 131 beds. It is sub-divided into Neonatal Intensive Care Unit, 3 stable baby wards and one Intermediate Ward. It also has a separate KMC ward. The MBU admits, on average, 15 babies per day and consequently 450 every month. It is well resourced with, equipment, drugs and well-trained specialist human resource that will enable high-quality care for preterm babies. The unit has sixteen incubators, 8 radiant warmers, and 12 Phototherapy stations, including 3 Firefly Phototherapy units and facilities for bedside measurement of bilirubin in additional to lab support. There is also equipment for newborn resuscitation with 2 Resuscitation stations, in addition to bags and masks, suction apparatus, and piped oxygen. Drugs such as Adrenaline and Phenobarbitone. IV fluids are also available. The unit is equipped with refrigerators that allow for short-term storage of breast milk where needed. There are 6 Senior Specialist Pediatricians who are experienced in newborn care, 5 Pediatric Residents, 11 House officers, 44 nurses and other support staff.

    The MBU is directly linked to the Obstetrics and the Gynaecology (O&G) Unit of the hospital by a corridor. This has been strategically designed to enable timely and seamless referral of babies between the two units and facilitate management of high-risk neonatal health complications. The O&G department is a 180 bed-capacity unit with a labour ward having 10 delivery beds. The O&G has a theatre for obstetric operations including caesarean sections. Review of records show that the number of infants born with birth weight 1.0 to <1.8 kg was around 50-70 per month.

    We currently have two forms of KMC. Mothers who are on admission on the Mother Baby Unit with Low Birth Weight Babies currently practice intermittent KMC Skin to Skin

Positioning, commencing when the baby is considered stable enough. We have no weight limits. This usually coincides with the starting of feeds or whenever the mother comes to the unit after delivery. This initial KMC is intermittent, with others coming to the Unit to do KMC 4 times a day for 2 hours at a stretch. We aim for (but do not always achieve!) 8 hours of Skin to skin positioning each day for each baby. We do this because inside the Unit the mothers do not have beds to sleep on so they sit on benches outside the ward. The situation will be the same when we move to our new Unit this month.

Babies, generally below 1.5kg, who need further support with KMC and feeding etc are moved down to our 8 bed KMC Unit for Continuous Skin to Skin positioning. There we aim to achieve at least 20 hours of skin to skin positioning a day. Mothers stay there for a variable length of time ranging from 3 days to one month depending on the baby's condition, weight gain etc. They are supervised by nurses and a doctor goes down once a day to see the babies.

Currently all mothers use their own pieces of cloth to tie their babies in skin to skin position, a strategy we have deliberately encouraged to avoid putting barriers in the way of the up scaling of KMC in Ghana

In addition to the Principal Investigator (Dr Samuel Newton, Public Health Specialist) and co-investigators from Paediatrics (Dr Gyikua Plange-Rhule, Prof Daniel Ansong (Paediatrics)and Dr Roderick Reindorf (Obstetrics), a number of research staff will be employed specifically for the project. An overall Trial Director/ coordinator Dr Ruth Owusu Ofori will be responsible for day to day oversight of all teams.

A total of four (4) trained Research Assistants (who are all degree holders or newly qualified nurses who have had previous experience in Data collection in the hospital) will work in shifts so that two of them are always available for screening and enrolment. Four (4) KMC support workers will be employed and trained to support women enrolled in the study to deliver the intervention. In addition, four research staff will collect outcome data, and two field staff will follow up those discharged at home.

18. **Description of process of identification of potential participants:** The Research Assistants will liaise with the doctors and nurses of the Antenatal clinicto identify pregnant women who are deemed to be at risk of preterm delivery or who are likely to give birth to a Low Birth Weight baby (such as those with high BP, anaemia, < 18 years age, identified Intrauterine Growth Retardation etc). When these mothers are identified, they will be given written information about the study and if they intend to deliver in KATH, they will be pre-consented about the study. In addition, the prenatal wards and the Pre eclamspsia wards (A4 and A1 Dark Room) will be visited at least twice a day by the Research Assistants to see if there are mothers who may have been admitted either for delivery of a preterm or LBW baby. If they identify such a mother, and she is in a position to be preconsented, they will do so. If not they will wait until after delivery. Dr Roderick Reindorf, a co-investigator in the study and an Obstetrician, together with other staff from the Department of Obstetrics and Gynecology will be our contact person(s)so that women can ask questions concerning the study.

19. **Complete description of consent (and assent process):** The process will be as exactly described in the master protocol.

All pregnant women admitted in hospital for delivery (including mothers who come in labour, and those coming for Caesarean Section or induction of labour, will be screened for the risk of delivering a low birth weight baby. This will typically occur at any of five places namely, the A4 Ward, the A1 Pre Eclampsia Ward, The Labour Ward and the Special Ward. The Research Assistants will constantly be visiting / calling these wards to find such mothers.

If after Research Assistant from the Screening and Enrollment Team (S&E RA) administers the Pre Screening Form, mother is likely to deliver a low birth weight baby, a Research Assistant from the Informed Consent Team (IC RA) will provide all the information about the study and seek her consent for participating in the study. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. After birth of the baby, and filling of the Screening Form by the S&E RA, if all the inclusion criteria are met and none of the exclusion criteria are present, the consent of the mother will be verbally confirmed in the labor room /Operation Theatre by the IC RA who is on duty for the study. This may or may not be the same person who administered consent depending on the timing of delivery.

In situations where a mother comes to deliver but is not in a condition to be consented before delivery, the Screening form will be applied immediately after birth by S&E RA and if the baby is eligible, the IC RA will administer consent to the mother after delivery. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. Mothers who consent only after delivery will be given the opportunity to decide on continued participation in the trial 24 hours after birth by a member of the Informed Consent Team using the Reconfirmation of Consent Form.

Mothers who are between 15 and up to 18 years of age will still be eligible for enrolment for this study if they are willing to do so. Assent from the mother will be obtained before recruitment but the consent form will be signed by the minor mother's Legal guardian who will also be fully taken through the Consent process by the IC RA.

If a woman or her Legal Guardian is illiterate, an impartial witness will be present during the entire informed consent process. The impartial witness will also sign and date the consent form, along with the individual who performed the informed consent discussion. All mothers considered to be at risk of delivering a small baby will be provided information about the study, and asked for consent for participation in the study in case they deliver a small baby who meets study eligibility criteria. Before taking consent, the treating physician or nurse/midwife will always be asked to certify that the woman is fit to provide consent.

20. Data Management:

g. The data management will be undertaken by Research and Development (R&D) department of the Komfo Anokye Teaching Hospital jointly. PI, Komfo Anokye Teaching Hospital &(R&D) will oversee the process.

h. The data collected at the site will be reviewed by PIs, Co-PIs and authorized designated staffs of Komfo Anokye Teaching Hospital as well as the R & D team. The study team will make available a list of authorised persons who can access the data and their level of access rights will be shared with WHO.

i. The data management will be as per the data management plan received from WHO.

j. R & D &KATH will be jointly responsible for storage of the data at clinical site/ R & D server (as per WHO directions and agreement).

k. Future Use & Destruction of the data will be done as per WHO / sponsor guidelines.

l. Routine Precautions to Protect Data Confidentiality will be taken care.

i. The subject research identification codes will be used
ii. Files containing electronic data will be password-protected and encrypted (at least when data are transferred or transported).
iii. Research data/specimens will be stored securely in locked cabinets or rooms.
iv. Electronic data will be stored in password-protected computers or files.
v. Consent and authorization forms will be stored securely in locked cabinets or rooms, separately from the research data.
vi. Research staff will be trained on the WHO ERC-approved SOP for managing and storing research data.

21. Data Analysis: The analysis will be done jointly in accordance with master protocol.

22. Sample Size: The sample size for comparison of two proportions (21.0% compared with 16.8%) is 2080 per group, thus a total of 4200 neonates will be required to be enrolled in all sites. Based on the number of neonates born in the selected hospitals, and assuming that we will be able to enroll about half of these births, enrolment can be completed in about two years.

COUNTRY/SITE	**Eligible 1.0-1.8kg infants**	**Expected enrolment per month**	**Expected enrolment in 2 years**
Ghana	50	25	600
India	140	70	1680
Malawi	50	25	600
Nigeria	30	15	360
Tanzania	80	40	960
Total	350	175	4200

23. Dissemination Strategy

a. The results of the study will be disseminated to all the health workers in KATH through a meeting.
b. Study participants will be informed about the results through a letter explaining the results in simple lay person language.

c. A national results dissemination meeting will be held within 3 months of completion of data analysis, which will be attended by relevant Ghana Health Service and the Ministry of Health at both local and national level, as well as professional associations.
d. The study outcomes will be reported at specific intervals, as agreed and approved by WHO. It may be published in peer-reviewed journals site specific and also with the multi country data.

24. Additional ethical considerations: As clinical site investigators, Ghana team do not foresee any additional ethical considerations and will ensure compliance with the protocol and project requirements outlined by WHO/ Sponsor. However, we will also abide by the applicable local regulations / hospital policies and standard of care for the management of the participants enrolled in this study.

25. Translated consent forms are attached

26. Local Ethical Approval is attached.

27. Budget of the site:

Year 1: US$ 260.901
Year 2: US$ 242,978
Year 3: US$ 187,892

28. The CVs of the investigators have been submitted with the Master Protocol.

Site-specific information – Malawi, Queen Elizabeth Central Hospital
(Annexure to Master Protocol version 3.0, 30 September 2017)

Introduction: The Immediate KMC study master protocol has already been approved by WHO ERC. This document is an Annexure to the immediate iKMC study master protocol, and provides additional information from Malawi site. We confirm that the study in Malawi site will fully conformed to the master protocol.

Additional Information:

29. The Malawi site of this multi-center study – Queen Elizabeth Central Hospital, Blantyre, Malawi – will adhere to all elements of the master protocol.

30. Study area:

The study will take place at the Queen Elizabeth Central Hospital in Blantyre, Malawi's main commercial city, situated in the southern region of the country. The site is a tertiary care referral center catering for the southern part of Malawi, mainly servicing lower and middle income families. Malawi has one of the world's highest premature delivery rates at 18%.

31. Description of site:

The study will be conducted in both the Obstetrics and Paediatrics departments of the Queen Elizabeth Central hospital, Blantyre, Malawi. Being a referral facility which receives high risk obstetric patients, the hospital has a high proportion of preterm and small for gestational age babies.

At Queen Elizabeth Central Hospital, all babies with a birth weight <2000g are sent to the NICU. Babies weighing ≥1800 and ≤2000g are briefly assessed by the medical and nursing staff in the NICU. If they are stable, the mothers are counselled on KMC and then the mother and baby are sent to the postnatal ward, to continue breastfeeding and Kangaroo Mother Care. All babies with a birthweight ≤800g are admitted in NICU. Care provided in NICU includes warmth, breast-milk feeding, and if required, intravenous fluids, parenteral antibiotics, oxygen, and continuous positive airway pressure. There is no surfactant therapy and mechanical ventilation. KMC is practiced in this hospital after achieving stabilization, usually after 3-7 days of age. Review of recent records from the hospital shows that the number of infants born with birth weight 1.0 to <1.8 kg averages around 50-80 per month.

The research team currently includes Dr Kondwani Kawaza as Principle Investigator and Dr Queen Dube as well as Dr Ausbert Msusa as Co-Investigators. Dr Dube is the Clinical Head of Department in Paediatrics at the Queen Elizabeth Central Hospital, while Dr Msusa is Deputy Academic Head in the department of Obstetrica and Gynaecology. Ms Patricia Siyabu, Nurse in-charge of the NICU is also part of the team, and has received TOT in IKMC at Sarfdarjung hospital, Delhi, India. A Project Coordinator and the rest of

the study staff will be employed for the project. An overall project coordinator will be responsible for overseeing day to day activities of all teams.

There will be a recruitment team of 10 research nurses, working in shifts. Twenty-four hours a day, one nurse will always be available for screening. He/she will identify all mothers at risk of delivering LBW babies (pre-screen) and obtain consent. They will cover antenatal clinic, antenatal wards and labour ward. Another study nurse will be stationed in the delivery areas (LW and theatre). He/she will be responsible for screening and assessment for eligibility for enrolment; obtaining informed consent, enrolment as well as randomization of enrolled cases.

Five research nurses will be employed to support women enrolled in the study deliver the intervention. Five nurses will also work in shifts, following up the enrolled women performing real time data recording as well as transcribing data from clinical records onto the study data collection forms. We will also employ 2 field workers who will conduct participant follow up, both in the KMC clinic and through home visits.

32. Description of process of identification of potential participants:

Potential participants will be identified from the antenatal clinic, the Antenatal wards, Gynecology wards as well as the labor wards at the Queen Elizabeth Central Hospital Obstetric unit. Mothers with high risk factors for low birth weight deliveries, will be given written information about the study, which has been translated into local vernacular (Chichewa). The attending doctor and midwife will brief the prospective mothers about the study.

33. Complete description of consent (and assent process):

The process will be as exactly described in the master protocol.

All pregnant women admitted in hospital for childbirth in labor, or before caesarean section, will be screened for the risk of delivering a low birth weight baby in the labor ward waiting room. If a mother is likely to deliver a low birth weight baby, Research Nurse 1 will provide all the information about the study and seek her consent for participating in the study. Before taking consent, the treating physician or clinician will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. After the baby is born, if all the inclusion criteria are met and none of the exclusion criteria are present, the mother's consent will be verbally confirmed in the labor room or Operating Theatre by the Research Nurse 2.

There will be occasions where a baby is born unexpectedly very small. In such a case, the Research Nurse 2 will have no alternative but to obtain consent from the mother soon after delivery. Again in this case, the treating physician or clinician will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent before obtaining the consent. Research Nurse 2 will follow up these mothers up to 24 hours after delivery, and give her the opportunity to decide about continued participation in the study.

Mothers who are minors will be eligible for enrolment in this study if they are at least 15 years of age. Assent from the mother will be obtained before recruitment but the consent form will be signed by the minor mother's guardian (parent).

If a woman is illiterate, an impartial witness will be present during the entire informed consent reading and discussion. The impartial witness will sign and date the consent form, along with the individual who conducted the informed consent discussion. All mothers considered to be at risk of delivering a small baby will be provided information about the study, and asked for consent for participation in the study in case they deliver a small baby who meets study eligibility criteria. Before taking consent, the treating physician or nurse/midwife will be asked to certify that the woman is physically, psychologically and emotionally fit to provide consent. The mothers will be asked to confirm their consent for participation in the study verbally within the first two hours after birth.

34. Data Management:

m. Data management will be undertaken by the University of Malawi College of Medicine Research Support Centre (RSC), in coordination with WHO. The local PI and Co-PIs from both the University of Malawi and Queen Elizabeth Central Hospital will oversee the process.

n. The data collected at the site will be reviewed by the PI, Co-PIs and authorized designated staff from the Research Support Centre. A list of authorized persons who can access the data and details of their level of access rights will be shared with WHO.

o. The data management will be as per the data management plan set up by and received from WHO.

p. The University of Malawi College of Medicine and the Queen Elizabeth Central Hospital will be jointly responsible for storage of the data at clinical site or RSC server (as per WHO directions and agreement).

q. Future Use & Destruction of the data will be done as per WHO / sponsor guidelines.

r. Routine Precautions to Protect Data Confidentiality will be employed.

i. The subject research identification codes will be used

ii. Files containing electronic data will be stored in password-protected computers and files and encrypted (at least when data are transferred or transported).

iii. Research data/specimens will be stored securely in locked cabinets or rooms.

iv. Consent and authorization forms will be stored securely in locked cabinets or rooms, separately from the research data.

v. Research staff will be trained on the WHO ERC-approved SOP for managing and storing research data.

35. Data Analysis:

The analysis will be done jointly in accordance with master protocol.

36. Sample Size:

The sample size for comparison of two proportions (21.0% compared with 16.8%) is 2080 per group, thus a total of 4200 neonates will be required to be enrolled in all sites. Based on the number of neonates born in the selected hospitals, and assuming that we will be able to enroll about half of these births, enrolment can be completed in about two years.

COUNTRY/SITE	Eligible 1.0-1.8kg infants	Expected enrolment per month	Expected enrolment in 2 years
Ghana	50	25	600

India	140	70	1680
Malawi	50	25	600
Nigeria	30	15	360
Tanzania	80	40	960
Total	350	175	4200

37. Dissemination Strategy:

a. The results of the study will be disseminated to all the health workers at Queen Elizabeth Central Hospital and University of Malawi College of Medicine through presentations at academic clinical meetings.
b. Study participants will be informed about the results through a brochure summarizing the results in simple lay person language.
c. A national results dissemination meeting will be held within 3 months of completion of data analysis, which will be attended by relevant Ministry of Health officials at both the central and state level, as well as professional associations.
d. The study outcomes will be reported at specific intervals, as agreed and approved by WHO. The site specific results will be published in peer-reviewed journals. The data will also be published as part of the multi country study results.

38. Additional ethical considerations:

The Malawi iKMC study team do not foresee any additional ethical considerations. We will ensure compliance with the protocol and project requirements outlined by WHO/ Sponsor. We will also abide by all the applicable local regulations, policies and standards of care for the management of the participants enrolled in this study.

39. Translated consent forms were sent as appendices in the Malawi IRB approved protocol.

40. Local Ethical Approval is: Approval certificate was submitted to WHO.

41. Budget of the site:

Year 1: US$ 325,329
Year 2: US$ 196,650
Year 3: US$ 120,072

42. The CVs of the investigators have been submitted with the Approved Protocol.