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CIRCULAR

Imphal, 23rd May, 2025

No. 95/RIMS-MRU/2025: The undersigned has received a letter from the Deputy Secretary, the Department of Health Research (DHR), Ministry of Health and Family Welfare (MoHFW), Government of India, wherein it is informed that as a novel initiative to strengthen the research ecosystem in the medical colleges and research institute across the country, monthly Research Grand Rounds will be organized as monthly webinars entitled 'Research Masterclass.'

2. The first session of the Research Masterclass is scheduled as follows:
Date: 30.05.2025 (Friday)
Time: 3:00 PM onwards
Join Zoom Meeting: https://echo.zoom.us/j/89155909409
Meeting ID: 891 5590 9409

3. It was also instructed to disseminate the information and ensure **maximum participation** in the Masterclass.

4. In this regard, the faculty members, researchers and PG students are requested to attend the first session of the Research Masterclass on **30.05.2025** without fail to attain maximum participation from the Institute.

5. The research papers to be discussed during the research masterclass are available in the RIMS website: https://www.rims.edu.in/secure/ . and also being shared to the concerned Department through their respective e-mail IDs.

6. This is issued with the approval of the Director, RIMS.

Encl.: Letter from the DHR

23-05-2025

Prof. T. Jeetenkumar Singh,
Nodal Officer,
Multi-Disciplinary Research Unit,
RIMS, Imphal

Copy to
1. P.S. to Director, RIMS for kind information of Director
2. P.A. to Medical Superintendent, RIMSH for kind information
3. The Dean (Academic), RIMS
4. The Principal, Dental College, RIMS
5. All HODs, RIMS Imphal.....
6. The Principal, College of Nursing, RIMS
7. Chairman, LRAC, MRU, RIMS
8. Members, LRAC, MRU, RIMS.....
9. Members, EC, MRU, RIMS, Imphal.....
10. All PIs/ Nodal officers/ Researches
11. IT section, RIMS, Imphal – for uploading the notice in the website
12. Office file

No. R.11016/22/2024-HR
Government of India
Ministry of Health & Family Welfare
Deptt of Health Research

IRCS Building, 2nd Floor,
Red Cross Road
New Delhi – 110 001
21.05.2025

To
The Dean/ Principal/ Director of Medical Colleges/ Institutes

Subject: Request to attend Research Masterclasses, 2025 for MRU network– reg.

Sir/Madam

I am directed to inform you that in recently concluded MRU conference 'Medical Colleges Research Connect 2025', Secretary, Department of Health Research (DHR) advised for organization of monthly Research Grand Rounds. It is a unique initiative to strengthen the research ecosystem in the medical colleges and research institutes across the country. The objectives of the Research Grand Rounds are as follows:

I. To deliberate on research methodologies, analytical tools, and emerging scientific approaches
II. To strengthen the methodological understanding amongst researchers needed to implement different kinds of research.
III. To foster collaboration and connectivity across research institutions

2. These Research Grand Rounds will be organized as monthly webinars entitled 'Research Masterclass' on last Friday of each month from 3:00-4:30 PM. The speakers for these Research Masterclasses will be eminent research scientists in the country who will be discussing their original research work in details from methodological point of view.

3. The first Research Masterclass is scheduled for 30.05.2025 (Friday) at 3:00 PM. The invited speaker is Prof. Suman P. Rao, Prof. & Head, Department of Neonatology, St John's Medical College Hospital, Bangalore, Karnataka. The research paper to be discussed during the research masterclass is enclosed with the letter. The link for the research masterclass is as follows: **https://echo.zoom.us/j/89155909409 (Meeting ID: 891 5590 9409)**.

4. Accordingly, it is requested to kindly disseminate the information in your institution and ensure maximum participation in Research Masterclass. Also, it is requested from your institute to share at least two questions related to research paper attached on the following email: **dhr-mru@gov.in** latest by 27.05.2025. These questions will be discussed with the speaker during masterclass.

Yours faithfully

(Dharkat R. Luikang)
Deputy Secretary

Copy to: The Nodal Officer of Multi-Disciplinary Research Units (MRUs)

WHO Immediate KMC Study Group *Trials* (2020) 21:280
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Trials

STUDY PROTOCOL Open Access

Impact of continuous Kangaroo Mother Care initiated immediately after birth (iKMC) on survival of newborns with birth weight between 1.0 to < 1.8 kg: study protocol for a randomized controlled trial

WHO Immediate KMC Study Group

Abstract

Background: Globally, about 15% of newborns are born with a low birth weight (LBW) as a result of preterm birth or intrauterine growth restriction or both. Up to 70% of neonatal deaths occur in this group within the first 3 days after birth. Kangaroo Mother Care (KMC) applied after stabilization of the infant has been shown to reduce mortality by 40% among hospitalized infants with a birth weight of less than 2.0 kg. In these studies, infants were randomly assigned and KMC was initiated after about 3 days of age, when the majority of neonatal deaths would have already occurred. The aim of this trial is to evaluate the safety and efficacy of continuous KMC initiated as soon as possible after birth compared with the current recommendation of initiating continuous KMC after stabilization in neonates with a birth weight between 1.0 and less than 1.8 kg.

Methods: This randomized controlled trial is being conducted in tertiary-care hospitals in five low- to middle-income countries (LMICs) in South Asia and sub-Saharan Africa. All pregnant women admitted to these hospitals for childbirth are pre-screened. After delivery, all neonates with a birth weight between 1.0 and less than 1.8 kg are screened for enrollment. Eligible infants are randomly assigned to intervention and control groups. The intervention consists of continuous skin-to-skin contact initiated as soon as possible after birth, promotion and support for early exclusive breastfeeding, and provision of health care for mother and baby with as little separation as possible. This efficacy trial will primarily evaluate the impact of KMC started immediately after birth on neonatal death (between enrollment and 72 h of age and deaths between enrollment and 28 days of age) and other key outcomes.

Discussion: This is the first large multi-country trial studying immediate KMC in LMICs. Implementation of this intervention has already resulted in an important enhancement of the paradigm shift in LMIC settings in which mothers are not separated from their baby in neonatal intensive care units (NICUs). The findings of this trial will have future global implications not only on how the LBW newborns are cared for immediately after birth but also for the dissemination of designing NICUs in accordance with the mother-neonatal intensive care unit (M-NICU) model.

Trial registration: Clinical Trials Registry - India (CTRI): CTRI/2018/08/01536 (retrospectively registered); Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12618001880235 (retrospectively registered).

Keywords: Immediate Kangaroo Mother Care (iKMC), Low-birth-weight babies, Mortality, Skin-to-skin contact, Breastfeeding, Mother-neonatal intensive care unit (M-NICU)

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1. Background

Globally, about 15% of infants are low birth weight (LBW) as a result of preterm birth or intrauterine growth retardation or both, and 60 to 80% of deaths in the neonatal period occur in these LBW infants [1–3]. The majority of neonatal deaths occur within the first 3 days of life. The causes of death among LBW infants include respiratory and brain complications, hypothermia, hypoglycemia, and infection [4, 5], which occur as a result of the immaturity of their lungs, brain, gastrointestinal tract, and skin.

Several interventions have been proven to be effective for improving survival of LBW infants, such as antenatal corticosteroids, breastfeeding, hygiene, case management of suspected infections, and hospital care of small babies, including Kangaroo Mother Care (KMC) [6]. The World Health Organization (WHO) defines KMC as the care of preterm and LBW infants where the mother keeps the baby in skin-to-skin contact (SSC) on her chest continuously until the baby no longer wants to stay in that position and she exclusively breastfeeds the baby [7]. Preterm infants have fundamental challenges to maintain thermoregulation and become cold very rapidly after birth and to a great extent this can be prevented by SSC. Evidence shows that KMC reduces mortality, possibly by helping maintenance of better thermoregulation, facilitating the earlier initiation of breastfeeding, reducing the risk of nosocomial infection, reducing the risk of apneic attacks, and promoting bonding of the mother–infant dyad [8–19].

The WHO publication *Kangaroo Mother Care: A Practical Guide* recommends initiation of short KMC sessions when the baby starts to recover, even if the baby still requires medical treatment such as intravenous fluids or oxygen [7]. It also recommends that continuous KMC should be initiated only after the baby is stable, meaning that the baby must be breathing spontaneously without additional oxygen. For the routine care of newborns weighing 2.0 kg or less at birth, the "WHO recommendations on interventions to improve preterm birth outcomes" recommend KMC, which should be initiated in health-care facilities as soon as the newborns are clinically stable [20]. These babies should be provided with as close to continuous KMC as possible. Currently, there is no recommendation for KMC for unstable neonates weighing less than 2.0 kg at birth.

A recently updated Cochrane review reported 40% lower mortality in infants with a birth weight of less than 2.0 kg who were given KMC as compared with those who were given standard (conventional) care in hospitals at 40–41 weeks' postmenstrual age (3.2% versus 5.3%; risk ratio (RR) 0.60, 95% confidence interval (CI) 0.39 to 0.92; eight trials, 1736 infants) [21]. 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; five trials, 1239 infants), a 30% improvement in exclusive breastfeeding at the end of neonatal period (RR 1.30, 95% CI 1.12 to 1.49: six trials, 711 infants), a shorter duration of hospital stay, and a higher prevalence, duration, and exclusivity of breast feeding [22]. In almost all studies included in the Cochrane review, KMC was initiated after the baby was clinically stable. For most studies, the median age at initiation of KMC was 3.2 to 24.5 days. Only in one study was KMC initiated before stabilization at a median age of 10 h [23]. 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 [24].

KMC cannot influence deaths that happen before its initiation. Thus, the 40% mortality impact of KMC in enrolled infants would translate in practice to only about 13% impact on mortality in all babies with a birth weight of less than 2.0 kg. Only 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], SSC from birth was associated with 100% stability scores in the fifth to sixth hour of life as compared with 46% in the conventional care group in newborns weighing 1.2–2.2 kg. A similar RCT from Vietnam in neonates weighing 1.5–2.5 kg reported significantly better transition to extra-uterine life (P <0.02) in the immediate SSC group. The neonates in the intervention group had significantly lower need for respiratory support, intravenous fluids, and antibiotic use during their hospital stay [26].

The impact of the KMC intervention could have been much larger had it been initiated immediately after birth. However, this has not been evaluated in LBW infants. Therefore, we aim to evaluate the safety and efficacy of continuous KMC initiated immediately after birth for neonates with a birth weight of 1.0 to less than 1.8 kg compared with initiating KMC after stabilization in improving survival. In this study, our main hypothesis is that those very small babies who are provided continuous KMC initiated immediately after birth will experience a reduced risk of death compared with a similar group in whom KMC is initiated only after stabilization.

2. Methods

2.1. Objectives and trial design

This is a multi-country, multi-center, non-blinded RCT to measure the effect of continuous KMC initiated immediately after birth on post-randomization mortality during the first 72 h of life and during the neonatal period, compared with continuous KMC initiated after stabilization, in infants with a birth weight of at least 1.0 and less than 1.8 kg born in hospitals in low- to middle-

income countries (LMICs). The secondary objectives are to determine the effect of the intervention on time to clinical stabilization, hypothermia, time taken to reach full breastfeeding, hypoglycemia, clinically suspected sepsis, time to hospital discharge, exclusive breastfeeding at the end of the neonatal period, maternal satisfaction with health care in the hospital, and maternal depression at the end of the neonatal period. The nature of the intervention makes blinding not possible.

2.2. Study setting

The study is being 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 were selected because they serve as referral centers capable of providing care to women at risk of delivering small babies and have a high proportion of LBW infants. In all of these hospitals, babies with a birth weight of less than 1.8 kg are routinely separated from the mother just after birth and provided care in neonatal intensive care units (NICUs). Care provided in NICUs includes warmth, breast-milk feeding as per availability, and (if required) intravenous fluids, parenteral antibiotics, oxygen, and continuous positive airway pressure (CPAP). There is limited or no access to more sophisticated interventions such as surfactant therapy and mechanical ventilation in most hospitals. Routine KMC is practiced in all of these hospitals and is initiated after achieving stabilization, usually after 3–7 days of age. The quality of care in the participating hospitals has been upgraded though the training of staff on the WHO minimum package of care for small babies. Identical weighing scales, mobile and fixed monitoring equipment, and CPAP equipment have also been provided to all sites, and training in their use was provided by a team of neonatologists.

2.3. Study population

All infants born alive in the participating hospitals with a birth weight from 1.0 to less than 1.8 kg, regardless of their gestational age, are eligible for participation in this trial with their mothers. The mother–infant pair is eligible even if the infants are twins or are born by caesarean section or if the mother experiences some complications during labor and delivery that are expected to be resolved within 3 days.

A mother–infant pair is not eligible if any of the following is present: (1) the mother is younger than 15 years of age, (2) the mother (or her guardian if the mother is 15–17 years old) is unable or unwilling to provide consent, (3) the mother is unlikely to be able to provide KMC within the first 3 days after birth (e.g., she has eclampsia or shock or has undergone major surgery), (4) the baby is unable to breathe spontaneously within 1 h of birth, (5) triplets or more, (6) the baby has a congenital malformation that interferes with the intervention or the intervention interferes with the required care for the congenital malformation, (7) the place of residence is not a part of the defined study area (the study area has been defined to make 28-day follow-up home visit feasible), or (8) if for any reason the mother–infant pair cannot be enrolled within 2 h of the birth of the infant.

2.4. Sample size calculation

Preliminary unpublished data obtained from the admission and discharge registers of the five selected hospitals show that neonatal mortality among infants with birth weights from 1.0 to less than 1.8 kg was about 32% in 2015. After improved implementation of the WHO-recommended minimum package of care for LBW infants in these hospitals, we expect mortality in the control group to fall by about one third (to be about 21%) during the study period. We calculated the sample size hypothesizing a 20% reduction in mortality (mortality in the control group: 21%; expected mortality in the intervention group: 16.8%) with a power of 90% and a significance level of 5%, allowing a maximum loss to follow-up of 10%. The sample size for comparison of two proportions is 2080 per group; thus, 4200 neonates are required to be enrolled.

2.5. The intervention

Formative research was conducted in each site to identify barriers to delivering and accepting the intervention and to develop and test solutions to overcome these. In this study, KMC is defined as continuous SSC with the mother or her surrogate aiming for at least 20 h per day, support for exclusive breastfeeding, and required medical care without separation from the mother as much as possible. The surrogate is a female relative or friend identified by the mother to provide SSC when she is unable to do so. Therefore, the intervention consists of three components:

1. *Promotion and support for continuous SSC initiated as soon as possible after birth*: Continuous SSC is initiated immediately after randomization, as soon as feasible after birth, aiming for at least 20 h a day. This is initiated by the mother or the surrogate within the delivery room or the operation theatre or on admission to the NICU and continued during transfer to the NICU and during the stay in the NICU. Mother and infant are kept in the neonatal unit until the infant meets predefined stability criteria. An infant is considered stable when he or she is breathing spontaneously with no oxygen or CPAP support at 40–60 breaths per minute,

maintaining oxygen saturation on room air more than 90%, does not have apnea, has a heart rate of 80 to fewer than 180 beats per minute, an axillary temperature of 36.0 to 37.4 °C and does not need intravenous fluids. After stabilization, the mother–infant dyad is shifted from the NICU to the KMC ward, where continuous KMC is provided until discharge from the hospital.

2. *Health care for mother and infant provided without separation*: The mother and infant are provided health care without separation as much as possible. Mothers are provided a place to sleep, food and health care by obstetric staff while in the NICU. If a mother has any complication for which she needs to be transferred to the obstetric ward or intensive care unit, SSC is continued with a surrogate until the mother becomes available. If the infant requires a procedure or treatment that is not possible in SSC, the infant is shifted to a cot or radiant warmer. SSC is temporarily interrupted for the period of the procedure or treatment and recommenced as soon as possible after that.
3. *Promotion and support for early and exclusive breastfeeding*: Mothers are encouraged and supported to put the infant to the breast when they are in the NICU. Even if the infant is unable to feed from the breast, putting the infant to the breast provides the infant the opportunity to learn how to attach and suckle. When possible, early expression and feeding of colostrum are carried out. A breastfeeding counsellor is available at all sites to help the mothers solve breastfeeding problems they face.

2.6. Comparator

Neonates randomly assigned to the control group receive conventional care, and in accordance with the routine at the sites, the mother and infant are separated until the baby is clinically stable. Except for the time of initiation of KMC, all other medical care is the same for intervention and comparison groups. When feeding can be started on the basis of the clinical condition of the baby, expressed breast milk is given using a feeding tube or cup and direct breastfeeding is started when the baby is ready. Short sessions of KMC are started for neonates randomly assigned to the control group when the baby is considered to be recovering (off CPAP, oxygen requirement of less than 30% and tolerating partial enteral feeds) and is at least 24 h old. The mother comes to the NICU to provide these brief sessions of KMC a few times a day during the time allocated for infant feeding. Continuous KMC is initiated for an infant randomly assigned to the comparison group when the infant meets stability criteria for at least a continuous period of 24 h and can be transferred to the KMC ward. As in the intervention group, mother and infant are kept in the neonatal unit until the infant meets the stability criteria. A minimum package of care for the neonates and the mothers is provided as a co-intervention for both the intervention and the control groups.

2.7. Primary and secondary outcomes

The primary outcomes of this study are mortality between enrollment and 72 h and mortality between enrollment and 28 days of age. Secondary outcomes are presented in Table 1. All outcomes are measured by using identical methods in the intervention and control groups by an independent outcome measurement team, which is not involved in the delivery of the intervention.

In addition, deaths from birth to 72 h of age of babies with a birth weight between 1.0 to less than 1.8 kg who are born in the participating hospitals but not enrolled in the study are reported. The schedule of outcome assessments is shown in Fig. 1.

Table 1 Primary and secondary outcomes

Primary outcome
The proportion of:
• Neonatal deaths between enrollment and 72 h of age measured through vital status records every 12 h during hospital stay
• Neonatal deaths between enrollment and 28 days of age measured through vital status records every 12 h during hospital stay and at a home visit on day 29 of age.
Secondary outcomes
The proportion of:
• Infants receiving exclusive breastfeeding (or exclusive breast-milk feeding) at the end of the neonatal period measured by 24-h feeding recall at a home visit on day 29 of age. (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 oral rehydration solution, if prescribed.)
• Infants with clinically suspected sepsis as per 12-hourly records during hospital stay.
• Infants with hypothermia defined as any axillary temperature of less than 36 °C from 2 h after randomization until discharge (or 28 days of age if not discharged before then).
• Infants with hypoglycemia defined as any blood glucose of less than 45 mg/dL (2.6 mmol/L) at mandatory measures at 6, 12, 18, and 24 h of age or at any other time.
• 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 as per 12-hourly records.
• Time to clinical stabilization: age at which the baby is considered to be clinically stable as per 12-hourly records and defined stability criteria.
• Maternal satisfaction with health care in the hospital as per interviews.
• Maternal depression defined as a score of 15 points or more in the Patient Health Questionnaire 9 (PHQ-9) administered to mothers at the day-29 home visit (Kroenke 2011).

		STUDY PERIOD							
	Pre-enrolment	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	Day of Hospital admission (for childbirth)	At birth	Within 2 hours of birth	Stay in NICU (until transfer out to KMC ward)			Stay in KMC ward (until discharge from hospital)	After hospital discharge until day 29	Day 29 after birth
				12 h of age	24 h of age	Every 12 h until transfer out of NICU	Every 12 h until discharge		
ENROLMENT:									
Pre-screening	X								
Informed consent	X								
Screening		X							
Confirmation of consent		X							
Allocation			X						
INTERVENTION:									
Intervention: Immediate KMC				X	X	X			
Control:									
Co intervention for both intervention and control groups:									
Minimum care package		X	X	X	X	X	X		
Continuous KMC after stabilization							X	X	
ASSESSMENTS:									
Mortality				X	X	X	X		X
Breastfeeding				X	X	X	X		X
Clinical sepsis				X	X	X	X		
Hypothermia				X	X	X	X		
Hypoglycemia				X	X				
Clinical Stabilization				X	X	X	X		
Maternal satisfaction							X (at discharge)		
Maternal depression									X

Fig. 1 Schedule of enrollment, interventions, and assessments for the Immediate Kangaroo Mother Care (IKMC) Study

2.8. Randomization

A computer-generated block randomization list with variable block size, stratified by site and by birth weight, has been prepared by a WHO statistician. The strata by birth weight are from 1.0 to less than 1.5 kg and from 1.5 to less than 1.8 kg. The random allocation is concealed in serially numbered, opaque, sealed envelopes prepared at the WHO and sent/delivered to the sites.

2.9. Blinding

The outcomes are assessed by an independent outcome measurement team which is not involved in the delivery of the intervention. However, the nature of the intervention prevents blinding of outcome assessors as they can observe whether the baby is with or without his or her mother in the NICU. Data analysts will be blinded to the allocation as far as possible.

2.10. Study implementation strategy

This clinical trial is conducted in compliance with the clinical trial protocol, good clinical practice, and the applicable regulatory requirements. The study is implemented in a standardized manner across all sites, and trial conduct is audited and monitored by quarterly visits by teams from the WHO. Fortnightly teleconferences track progress in the study and help to ensure ongoing harmonization. A full-time site trial coordinator at each site is responsible for the conduct of the trial. Three independent teams at each site are responsible for (i) screening and enrollment, (ii) KMC intervention support,

and (iii) outcome measurement. Each team member has been trained in standard operating procedures relevant for their work.

2.11. The screening and enrollment team

2.11.1. Pre-screening

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 of 1.0 to less than 1.8 kg and no exclusion criteria) mean that the final confirmation of consent needs to be taken in the minutes after birth. The screening and enrollment team therefore "pre-screens" all pregnant women admitted for childbirth (including those who plan to have a caesarian section delivery) if they are not in advanced stages of labor and identifies pregnant women who are at high risk of delivering an LBW infant. Women with a gestational age of less than 37 weeks, intrauterine growth restriction based on second- or third-trimester ultrasound, age of less than 18 years, height of less than 1.50 m, multiple pregnancy, pre-eclampsia or eclampsia, severe anemia, or fundal height of less than 32 cm are identified as "high risk" for delivering an LBW infant. The research assistant approaches such pregnant women, informs them about the study, and invites them to participate in the study. Before taking consent, the treating physician or nurse/midwife is asked to certify that the woman is physically, psychologically, and emotionally fit to provide consent. Additionally, consenting mothers are asked to identify one or two adult women relatives or friends of their choice who could act as their surrogates for providing SSC when and if they are not able to do so. Surrogates have their role in the study explained to them if the mother–infant pair is randomly assigned to the intervention group.

2.11.2. Screening

Health-care staff and a research assistant weigh every baby born in the hospital; the latter completes a screening form to assess whether the dyad meets all inclusion criteria and does not have any exclusion criteria. If mother and baby are eligible and the mother has consented prior to delivery, her consent is confirmed verbally before she and the infant are enrolled.

In situations where an infant is unexpectedly born very small (pre-screening either not carried out or if the pre-screening did not identify the pregnant woman as high risk), consent is obtained within the first 2 h of birth if the treating physician or nurse/midwife certifies that the woman is physically, psychologically, and emotionally fit. The mothers who consent after delivery are given another opportunity to decide about continued participation in the trial 24 h after birth. Mothers who are minors are eligible for enrollment in this study if they are at least 15 years of age and their consent is confirmed by the guardian (parent or husband). Women who undergo cesarean section and have not consented previously are not approached after delivery.

Recruitment of an adequate number of participants is ensured by pre-screening every pregnant woman admitted for child birth and screening every newborn born in the hospital. Inclusion of large public referral hospitals in the study and the proposed recruitment period of 2 years aim to ensure that the target sample size is adequately met. The WHO coordination team keeps a close watch on the progress of recruitment through two-weekly teleconferences.

2.11.3. Enrollment and Randomization

The research assistant opens a sealed, opaque envelope with the study identification number, which has the group allocation inside, and records the assignment of the mother–infant pair to intervention or control groups. The research assistant informs the KMC support research assistant about the allocation.

2.12. KMC intervention support team

2.12.1. Initiation of care according to group allocation

If the infant is allocated to the intervention group, the KMC support research assistant who attends all deliveries of potential babies helps 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 is carried out by using a pulse oximeter. The KMC support research assistant also helps to transfer the mother (or surrogate) and the baby to the NICU in SSC. The research assistant continues to support the mother or surrogate to provide continuous KMC after the baby is admitted to the NICU.

The infant is kept in SSC as much as possible, preferably with the mother but with a surrogate for the time when the mother cannot provide the intervention. In KMC, the infant is put naked on the mother's chest. The infant has a cap, diaper, and socks and is secured firmly to the chest with a binder that ensures a patent airway and a shirt that provides containment in the fetal position. All routine care is provided in SSC. Any interruptions in SSC are documented to determine the duration for which the intervention was provided per day. The KMC research assistant also supports the mother in early expression of milk and to help the baby suckle at the breast.

If the infant is allocated to the control group, routine care is provided by hospital staff. The infant is transferred to the NICU as soon as possible. When discharged from the delivery room or operation theatre, the mother is transferred to the postnatal ward and the infant remains in the NICU in accordance with current guidelines. When the infant is ready to be fed, the mother provides expressed breast milk. When the infant is recovering, the mother provides brief sessions of KMC in the NICU in accordance with current WHO guidelines.

2.13. Outcome measure team

2.13.1. Data collection

The research team assesses outcomes in the intervention and control groups by using identical methods and procedures. This independent team is not involved with the intervention delivery. Outcome measurement during hospital stay is through review of medical records (medical notes and treatment and feeding charts), interview with mothers, observation of the care given, and assessment of the baby, conducted every 12 h in the NICU and KMC ward. All forms completed by the outcome measurement, screening, and enrollment teams are entered in an electronic platform. Data range and consistency checks are incorporated into the data entry system. Facility-based data collection occurs up to hospital discharge. Several measures are in place to ensure participant retention and complete follow-up. When the mother–infant pair is ready for discharge from the hospital, field assistants accompany mother and baby home to get global positioning system (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 the last follow-up visit. This team builds and retains a strong rapport with the families to know their whereabouts during the follow-up periods. A home visit is conducted on day 29 of age to ascertain outcomes at the end of the neonatal period.

For those participants who withdraw from the study, the only data collected after withdrawal consist of in-hospital mortality.

Comprehensive monitoring of the safety of the study participants is performed throughout the course of the trial, from enrollment until the day-29 follow-up. Death of an enrolled baby is reported as a serious adverse event, and specific consideration is given for any factor potentially related to intervention. The investigator is responsible for informing the relevant local authorities, institutional review boards, or committees in accordance with their rules and standards. Once a report of an unexpected death is received, the WHO team informs the trial data and safety monitoring board (DSMB) within 24 h of receiving the information, and a final and detailed report is made within 1 week. The DSMB reviews these cases and makes recommendations regarding safety concerns and continuation of the study.

2.14. Monitoring of enrolled newborns

Every infant in the NICU is monitored, and information regarding temperature, heart rate, respiratory rate, and oxygen saturation is recorded every 6 h. Blood sugar similarly is monitored every 6 h during the first 24 h after birth and thereafter as and when required. In the KMC ward, infants are evaluated every 12 h up to hospital discharge. If signs of clinical deterioration are seen at any monitoring visit, the diagnosis of possible serious bacterial infection is considered.

2.15. Care for mothers

Unstable mothers or mothers who require special care are not transferred to the NICU. They continue to be managed in the intensive care unit or postnatal ward in accordance with usual hospital practice. The mothers are only transferred to the NICU for providing KMC once they no longer require special care.

Obstetric staff is responsible for providing postpartum monitoring and care for all mothers. If a mother is allocated to intervention, she receives routine postnatal care, including medical rounds, examinations, and medication, in the neonatal unit. A minimum care package for mothers is introduced for the postnatal care for mothers in both groups regardless of where they are located. The NICU nursing staff provides support in case of any emergency (such as secondary postpartum hemorrhage) and contacts the obstetric staff to provide definitive care.

2.16. Quality assurance

2.16.1. Training and standardization

Health-care staff in the delivery room, neonatal unit, and KMC ward is trained to provide the neonatal care using the minimum care package for both the neonates and the mothers. All relevant staff of the neonatal unit and KMC ward as well as the KMC support research assistants are trained to support KMC for very small infants by the technical support team from Karolinska Institute. This includes how to secure them with the wrap to maintain the baby's head in a safe 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 are also regularly trained in a standardized manual of operations for the study. All research staff is 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, have been carried out for all sites to ensure quality of study is maintained.

All research team members recruited for the study activities are well qualified and undergo intensive initial training. Their activities are supervised by competent trained study supervisors who support adherence to the manual of operations. The eligibility criteria and the outcomes to be assessed are very clearly defined in the manual of operations and the staff is trained and retrained regularly for that. The infant weighing scale is calibrated daily to minimize measurement errors. Internal quality checks are conducted by the trial coordinators and study principal investigators (PIs) at each site. The two types of quality checks are supervised observations and random independent checks. For the former, each research assistant is accompanied by the trial coordinator/PI for an activity each week. For the latter, 5% of observations are independently checked by the trial coordinator/PI.

All participating hospitals are supported to make quality-of-care improvements so they can implement the WHO Essential Care for Small Babies more effectively. The standard of care in accordance with the WHO manual for small infants includes monitoring, thermal control, breast-milk feeding support, and attention to hygiene for all infants. It also includes access to intravenous fluids, antibiotic therapy, and respiratory support with safe oxygen supplementation and bubble CPAP if required.

2.17. Trial registration

This trial is registered in two trial registries. The trial was first submitted for registration to Clinical Trials Registry - India (CTRI) in December 2017 as the India site was the first to be ready for implementation. It took a few months for clarifications and query resolution, and eventually the trial was retrospectively registered in CTRI (number: CTRI/2018/08/015369) on 17 August 2018. The trial was also registered in Australian New Zealand Clinical Trials Registry (ANZCTR) on 19 November 2018 once all of the African sites were enrolling in the trial (reference number: ACTRN12618001880235).

2.18. General principles for analysis

The primary analysis will be executed according to intention to treat. Even if KMC is discontinued because of clinical conditions of the mother or infant, 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 by using Consolidated Standards of Reporting Trials (CONSORT) statement.

2.19. Flow of participants

The flow and number of participants through assessment of eligibility, randomization, follow-up, and analysis are documented (Fig. 2). Reasons for exclusions and withdrawals are described.

2.20. Comparability of participants in the two groups

Descriptors for background characteristics in the intervention and control groups will be presented in a baseline table and summarized as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. These data will represent maternal age, parents' schooling, family income, household characteristics, mode of delivery, birth weight, Apgar score, and age at randomization. Although our large sample size is likely to yield a balance between the two study arms in the main analyses, we will carefully evaluate the size of any baseline imbalance in our planned subgroup analyses. Imbalanced characteristics that predict death will be appropriately adjusted for statistically.

A second analysis comparing quality of care will be performed to ensure that the minimum package of care is offered equally to both intervention and control groups and that the intervention is delivered as planned. These will include time between birth to initiation of KMC and place of care in the delivery room or operating theatre until transfer to the NICU. Additionally, infants' condition at the time of arrival to the NICU will be compared between groups.

2.21. Main effects

Effect sizes and their 95% CIs 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 RRs and their CIs. If loss to follow-up for primary outcomes is greater than 2.5%, hazard ratios and their CIs 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.

2.22. Subgroup analysis

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

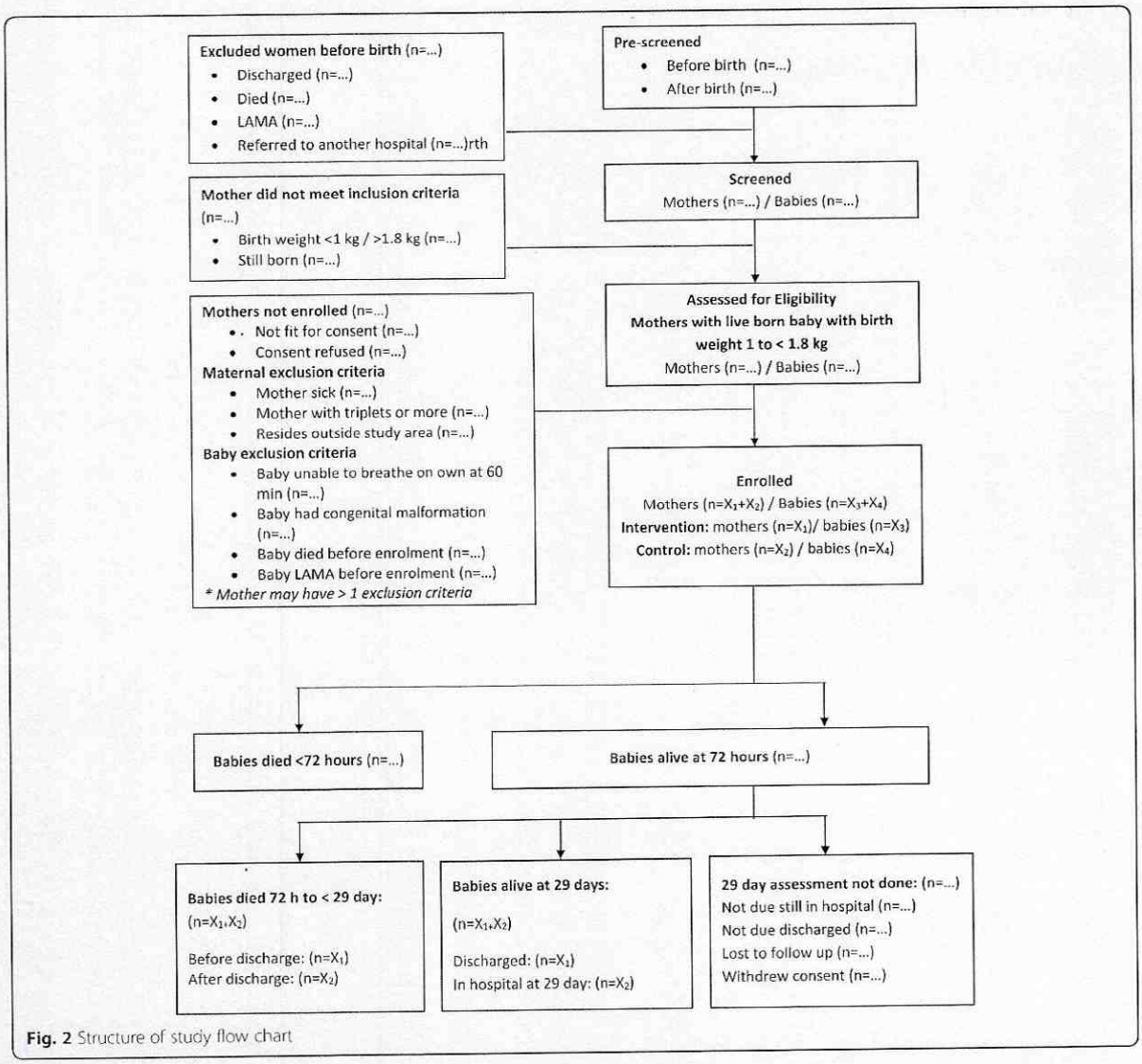

Fig. 2 Structure of study flow chart

A secondary analysis stratified by compliance to immediate KMC (iKMC) over 72 h of age will be carried out. This analysis will report on efficacy of the intervention by average duration of SSC, classified as more than 20 h per day, 10–19 h per day, and less than 10 h per day. In this secondary analysis, reverse causality may be an important issue because severely ill newborns may receive less or no SSC. To reduce the possibility of reverse causality, in a sub-analysis we will exclude the babies who show signs of severe illness in the first 6 h of life.

2.23. Trial oversight

The trial steering committee is composed of all PIs from study sites, Karolinska Institute study consultants, and WHO technical staff functioning as its secretariat. This committee is responsible for designing and implementing the study in a harmonized way.

An independent DSMB has been established by the WHO. The DSMB includes seven members with expertise in clinical trials, statistics, newborn care, and ethics in resource-limited settings. The DSMB also serves as the technical advisory group for the trial. The DSMB is responsible for safeguarding the interests of trial participants, potential participants, investigators, and sponsors; assessing the safety and early efficacy of the trial's intervention according to data available at a predefined schedule; monitoring the trial's overall conduct and quality and protecting its validity and credibility; and making recommendations concerning continuation/termination of study

determined by using O'Brien–Fleming stopping boundaries for early benefit/harm or futility. It also serves and advises the WHO and the PIs on the implementation of the trial. The members are independent of the trial and serve in their individual capacity. When about half of the enrollment is completed in the study, the DSMB will review an interim data analysis by arm to determine whether stopping boundaries have been crossed. The study protocol conforms to the SPIRIT checklist (Additional file 1).

3. Discussion

Upon completion, this trial will provide comprehensive data on safety and efficacy of iKMC in unstable LBW infants (birth weight of 1.0 kg to less than 1.8 kg) in developing countries. Furthermore, it will provide definitive answers on the impact of iKMC on neonatal mortality and on various outcomes in LBW infants, which will have implications for provision of clinical care. So far, KMC is recommended only for "stable" LBW infants. If the hypothesis is supported, this trial is likely to bring about a global paradigm shift in the intensive care of LBW infants.

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 is generally not accurate and very few women have an ultrasound in early pregnancy, (2) there is high incidence of small-for-gestational-age infants who are also at a high risk of death and could benefit from SSC, and (3) it is relatively easy to have accurate measurement of birth weight.

Infants with a birth weight below 1.0 kg have reduced chances of survival even in high-resource settings with sophisticated neonatal intensive care. The intervention would be difficult to implement in infants with extremely LBW. Babies with birth weights of 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. They should be provided KMC based on current recommendation.

The iKMC trial is unique in several respects. First, it is a pragmatic trial conducted in the real-life scenario of public sector neonatal units in LMICs. The intervention is provided using existing clinical staff in these units, and research nurses are involved only in collection of the research data. Moreover, the trial uses exclusive clinical inclusion criteria and examines important clinical outcomes such as death, sepsis, and breastfeeding rates. The participating centers in the trial were carefully selected to ensure that representation from most of the LMICs and results would be applicable to the vast majority of public sector neonatal units in LMICs.

Second, a minimum level of quality of care for the neonates and their mothers is ensured in the trial by implementation and monitoring of the minimum care package in all study hospitals. This includes care and resuscitation at birth, thermal care, provision of CPAP or other adequate and safe respiratory support as needed, breastfeeding support, monitoring, prevention of infections, and management.

Third, the trial, while evaluating whether iKMC adds to the benefit of standard KMC for LBW survival, brings about a global paradigm shift of zero separation of mothers from their babies by introducing the concept of mother-neonatal intensive care unit (M-NICU). Continuous KMC for both groups is promoted and supported after they are transferred out of the M-NICU/NICU. This requires a higher level of collaboration between obstetric and neonatal departments.

If the trial demonstrates the safety and efficacy of iKMC in LMIC settings with reasonable intensive care facilities, the next logical step would be to scale up the intervention and implement M-NICUs across LMICs. The results from this trial would have implications for high income countries that routinely practice separation of mothers from their babies. Implementation of immediate KMC in these high income countries where newborn mortality is relatively low could improve the quality of non-mortality outcomes such as improved breastfeeding rates, maternal bonding, and long term child development outcomes.

3.1. Trial status

The trial is ongoing in all five sites: Ghana, India, Malawi, Nigeria, and Tanzania. The first participant was recruited on 1 December 2017. Participant recruitment is expected to be completed by September 2020. The current protocol is version 3.4, dated 29 March 2018.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-020-4101-1.

Additional file 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Checklist.

Abbreviations

CI: Confidence interval; CPAP: Continuous positive airway pressure; CTRI: Clinical Trials Registry - India; DSMB: Data safety monitoring board; iKMC: Immediate Kangaroo Mother Care; KMC: Kangaroo Mother Care; LBW: Low birth weight; LMIC: Low- to middle-income country; M-NICU: Mother-neonatal intensive care unit; NICU: Neonatal intensive care unit; PI: Principal investigator; RCT: Randomized controlled trial; RR: Risk ratio; SSC: Skin-to-skin contact; WHO: World Health Organization

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including Prof. Betty Kirkwood (Chair), Prof. Elizabeth Molyneux, Prof Ravindra Mohan Pandey, Prof Siddarth Ramji, Prof Esther Mwaikambo, Prof. Olugbenga Mokuolu, and Ms. Charlotte Tawiah.

Provisions for post-trial care

There is no anticipated harm. The trial is covered by an insurance that will provide compensation for any unexpected harm resulting from trial participation.

Dissemination policy

The findings from the study will be disseminated through formal meetings with stakeholders where the final report will be presented. Data will also be presented in various international conferences and published in peer-reviewed journals.

Authors' contributions

All authors contributed to the drafting of the manuscript, reviewed the manuscript for intellectual content, approved the final version of the report, and have agreed to publication. All named authors adhere to the authorship guidelines of *Trials*.

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Availability of data and materials
The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study protocol is approved by the WHO Ethics Review Committee (reference number: EC0002910 approved on 6 October 2017). Approvals on the same protocol were also obtained from local institutional review boards in the five sites: Ghana's School of Medical Science/Komfo Anokye Teaching Hospital (reference number: CHRPE/AP/372/17, initial approval on 30 June 2017), Tanzania's National Institute for Medical research (reference number: NIMR/HQ/R.8a/Vol. IX/2621, initial approval on 6 November 2017), Malawi's College of Medicine Research and Ethics Committee (COMREC) (reference number: P.08/17/2235, initial approval on 27 September 2017), Nigeria's OAUTHC Ethics and Research Committee (reference number: IRB/IEC/0004553 NHREC/27/02/2009a, initial approval on 12 July 2017), Institute of Ethics Committee of VMMC & Safdarjung Hospital (reference number: IEC/SJH/VMMC/Project/August-2017, initial approval on 24 August 2017). Each updated version of the approved protocol will be submitted to the ethics committees above.
Written informed consent is taken by study staff from admitted pregnant women who are identified to be at high risk of delivering an LBW infant. The participants' confidentiality is maintained throughout the trial in line with the standard International Conference on Harmonization - Good Clinical Practice (ICH-GCP) principles. The consent form includes consent for participation in the trial and also for sharing of data with researchers. This study does not involve collection of biological specimens. The consent forms are held by the study teams at the five sites and are available for review by the Editor-in-Chief of this journal.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

ORIGINAL ARTICLE

Immediate "Kangaroo Mother Care" and Survival of Infants with Low Birth Weight

WHO Immediate KMC Study Group*

ABSTRACT

BACKGROUND

"Kangaroo mother care," a type of newborn care involving skin-to-skin contact with the mother or other caregiver, reduces mortality in infants with low birth weight (<2.0 kg) when initiated after stabilization, but the majority of deaths occur before stabilization. The safety and efficacy of kangaroo mother care initiated soon after birth among infants with low birth weight are uncertain.

METHODS

We conducted a randomized, controlled trial in five hospitals in Ghana, India, Malawi, Nigeria, and Tanzania involving infants with a birth weight between 1.0 and 1.799 kg who were assigned to receive immediate kangaroo mother care (intervention) or conventional care in an incubator or a radiant warmer until their condition stabilized and kangaroo mother care thereafter (control). The primary outcomes were death in the neonatal period (the first 28 days of life) and in the first 72 hours of life.

RESULTS

A total of 3211 infants and their mothers were randomly assigned to the intervention group (1609 infants with their mothers) or the control group (1602 infants with their mothers). The median daily duration of skin-to-skin contact in the neonatal intensive care unit was 16.9 hours (interquartile range, 13.0 to 19.7) in the intervention group and 1.5 hours (interquartile range, 0.3 to 3.3) in the control group. Neonatal death occurred in the first 28 days in 191 infants in the intervention group (12.0%) and in 249 infants in the control group (15.7%) (relative risk of death, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P=0.001); neonatal death in the first 72 hours of life occurred in 74 infants in the intervention group (4.6%) and in 92 infants in the control group (5.8%) (relative risk of death, 0.77; 95% CI, 0.58 to 1.04; P=0.09). The trial was stopped early on the recommendation of the data and safety monitoring board owing to the finding of reduced mortality among infants receiving immediate kangaroo mother care.

CONCLUSIONS

Among infants with a birth weight between 1.0 and 1.799 kg, those who received immediate kangaroo mother care had lower mortality at 28 days than those who received conventional care with kangaroo mother care initiated after stabilization; the between-group difference favoring immediate kangaroo mother care at 72 hours was not significant. (Funded by the Bill and Melinda Gates Foundation; Australian New Zealand Clinical Trials Registry number, ACTRN12618001880235; Clinical Trials Registry-India number, CTRI/2018/08/015369.)

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*A complete list of the collaborators in the WHO Immediate KMC Study is provided in the Supplementary Appendix, available at NEJM.org.

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Infants with low birth weight who are born preterm, are small for their gestational age, or both constitute approximately 15% of all neonates worldwide but account for 70% of all neonatal deaths. Reducing mortality among these infants, particularly those born in low- and middle-income countries in Asia and sub-Saharan Africa, is therefore key to the achievement of the United Nations Sustainable Development Goals target of reducing neonatal mortality to a level at least as low as 12 deaths per 1000 live births in all countries by 2030.[1-3]

"Kangaroo mother care," defined as both continuous skin-to-skin contact of the infant with the chest of the mother (or another caregiver when not possible with the mother) and feeding exclusively with breast milk, is among the most effective interventions for preventing death in infants with low birth weight.[4] World Health Organization (WHO)[5] guidelines currently recommend initiation of short, intermittent sessions of kangaroo mother care when the infant's condition begins to stabilize and continuous kangaroo mother care when the infant's condition has stabilized. In a meta-analysis of eight hospital trials involving a total of 1736 infants, infants who received kangaroo mother care after stabilization had a 40% lower mortality than those who received conventional care in an incubator or a radiant warmer (3.2% vs. 5.3%; risk ratio, 0.60; 95% CI, 0.39 to 0.92).[6] This meta-analysis also showed that infants who received kangaroo mother care had fewer infections, higher rates of exclusive breast-feeding, and better weight gain than those who did not. In studies included in the review, the mean age at randomization (when the condition of the infants was considered to be stable) ranged from 10 hours to 24.5 days of life. Approximately 45% of neonatal deaths occur within 24 hours after birth and 80% during the first week of life[7]; thus, the majority of deaths among infants with low birth weight typically occur before kangaroo mother care can be initiated.

The effect of initiating kangaroo mother care immediately after birth on physiological stabilization has been evaluated in two randomized, controlled trials conducted in South Africa[8] and Vietnam.[9] In both trials, skin-to-skin contact that was initiated soon after birth in infants with low birth weight resulted in earlier stabilization than conventional care.

There is a critical knowledge gap regarding the effect of initiating continuous kangaroo mother care soon after birth and before stabilization with respect to mortality in infants with low birth weight. We conducted a large, multicenter, randomized, controlled trial to evaluate the safety and efficacy of continuous kangaroo mother care initiated immediately after birth in infants with a birth weight between 1.0 and 1.799 kg.

METHODS

STUDY DESIGN AND PARTICIPANTS

The trial was conducted in five tertiary-level hospitals in Ghana, India, Malawi, Nigeria, and Tanzania. All live-born infants in the participating hospitals whose birth weight was between 1.0 and 1.799 kg, regardless of gestational age, type of delivery, or singleton or twin status, were eligible for inclusion. Mother–infant pairs were excluded if the mother was younger than 15 years of age, was unable or unwilling to provide consent, had given birth to three or more infants in this pregnancy, was sick and unlikely to be able to provide kangaroo mother care within the first 3 days after birth, could not be enrolled within 2 hours after childbirth, or resided outside the study area. Infants who were unable to breathe spontaneously by 1 hour after birth or who had a major congenital malformation were also excluded.

The trial was approved by the ethics review committee at WHO and at each study site. The study was overseen by a steering committee and a data and safety monitoring board. Drs. Bahl, Rao, Yoshida, and Minckas vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. The details of the study methods have been published previously and are briefly summarized here.[10]

PROCEDURES

Three independent teams, trained in the standard operating procedures of the study, were responsible for the conduct of screening and enrollment, the provision of support for the mothers providing kangaroo mother care, and the measurement of outcomes at each site. Prescreening of all pregnant women admitted for childbirth was conducted to identify women at

high risk for delivery of a low-birth-weight infant, and consent for study participation was sought. All infants born in the hospital were weighed and screened for eligibility. If the mother and infant were eligible for study participation, consent was confirmed if it had already been obtained before birth. If consent had not been obtained before birth, it was obtained after birth. At enrollment, mothers were asked to identify one or two adult women who could act as surrogate providers of kangaroo mother care; only women are permitted to stay in the postnatal areas in all study hospitals.

Randomization was performed with the use of computer-generated blocks. The blocks were variable in size and were stratified according to site and birth weight (1.0 to 1.499 kg or 1.5 to 1.799 kg). The assignments were sealed in serially numbered, opaque envelopes prepared at WHO and delivered to the sites. Research assistants conducted randomization as they opened each numbered envelope sequentially. Twins were allocated to the same group. The nature of the intervention prevented blinding, but the outcome assessment was conducted by an independent team whose members were not involved in intervention delivery.

Changes in the nature of obstetrical and neonatal care as well as structural changes in the neonatal intensive care units (NICUs) were necessary for mothers providing immediate kangaroo mother care. These NICUs (hereafter referred to as Mother–NICUs), which included mothers' beds and reclining chairs, were built or converted from existing NICUs. All equipment, staff, and care provision in the Mother–NICUs remained the same as in the control NICUs. At two sites, completely new Mother–NICUs were built in a nearby location and the existing NICUs were retained as the control NICUs. At the other three sites, modifications were made to convert half the existing NICUs to Mother–NICUs, and the other half served as the control NICUs. Infants receiving kangaroo mother care were secured firmly to the mother's chest with a binder that ensured a patent airway.[11] All care of the mother and infant was provided while skin-to-skin contact was maintained, if possible, and all interruptions in kangaroo mother care were documented. Obstetricians supervised essential postpartum care provided to mothers in the Mother–NICUs, just as they did for mothers in the control NICUs.

Infants who were assigned to the control group were transferred to the control NICU without their mother, in accordance with standard practice. Mothers provided expressed breast milk and participated in brief sessions of kangaroo mother care when their infant began to recover from preterm birth complications and was at least 24 hours old.

Hospital staff provided care for all infants enrolled in the study, in accordance with the WHO minimum-care package for small infants.[12] In both the intervention and control groups, once infants were clinically stable (as determined on the basis of prespecified criteria)[10] for 24 hours, they were transferred from the Mother–NICU or the control NICU to the kangaroo mother care ward, where continuous kangaroo mother care was provided for all infants until discharge.

OUTCOMES

The primary outcomes were mortality from enrollment to 28 days of age and mortality from enrollment to 72 hours of age. The secondary outcomes included hypothermia (any axillary temperature <36°C), hypoglycemia (any blood glucose level of <45 mg per deciliter, measured when clinically indicated), suspected sepsis, time to clinical stabilization, exclusive breast-feeding (only by suckling) at the time of discharge, exclusive breast-feeding at the end of the neonatal period (at 28 days of age), maternal satisfaction with care, and maternal depression (see Table S1 in the Supplementary Appendix, available at NEJM.org).[10] In addition, death from the time of birth to 72 hours in unenrolled infants weighing between 1.0 and 1.799 kg, was documented. The only serious adverse event assessed according to the protocol was death.

Outcome data were collected with the use of the same methods and procedures for all enrolled infants. Clinical monitoring was conducted every 6 hours for all infants while they were in the Mother–NICU or the control NICU. Information on the duration of skin-to-skin contact and the duration of hospital stay was collected by research assistants. A home visit was conducted on day 29 to obtain data on survival, breast-feeding, and maternal depression.

STATISTICAL ANALYSIS

We estimated that 4200 infants were needed to detect 20% lower mortality in the intervention group than in the control group (16.8% vs. 21.1%), with a 95% confidence level, 90% power, and a 10% loss to follow-up. The data and safety monitoring board conducted interim analyses when 50% and 75% of the participants had been enrolled. After the second interim analysis, the data and safety monitoring board recommended stopping enrollment in the trial because of the clear benefit in neonatal survival in the infants receiving immediate kangaroo mother care (see the Supplementary Appendix).

Intention-to-treat analyses were performed for the primary and secondary outcomes,[10] and risk ratios and 95% confidence intervals were calculated for these outcomes. Adjusted risk ratios were estimated with the use of log-binomial regression modeling controlled for clustering due to multiple births and other important baseline characteristics that had the potential to be confounders. Hazard ratios were calculated with the use of multivariable Cox survival analysis to compare the times to clinical stabilization in the two groups. We used marginal mean imputation for missing values in continuous covariates and the most frequent response to impute categorical variables. No imputation was made for the primary outcomes.

Prespecified subgroup analyses were performed to explore modification of effect of immediate kangaroo mother care on primary outcomes according to birth weight (1.0 to 1.199 kg, 1.2 to 1.499 kg, and 1.5 to 1.799 kg), gestational age (<31 weeks, 31 to <34 weeks, 34 to <37 weeks, and ≥37 weeks), type of delivery (vaginal birth or cesarean section), singleton or twin gestation, and size for gestational age (small for gestational age or not small for gestational age).[10] Subgroup analyses according to site were conducted post hoc. In the intervention group, we examined the primary outcomes in subgroups according to compliance with kangaroo mother care (skin-to-skin contact for ≥20 hours, 10 to <20 hours, or <10 hours per day). To address reverse causality in this analysis, we excluded infants with any sign of severe illness in the first 6 hours of life. Causes of death were assigned by investigators on the basis of clinical information regarding hospital deaths and of interviews with mothers in their homes for deaths that occurred after discharge.

Post hoc analyses were conducted to explore the effect of the intervention on breast-feeding during the hospital stay. These analyses included assessments of the proportion of newborns by group who initiated breast-feeding within 24 hours, were put to breast in the first 72 hours, reached full breast-feeding within 7 days, and were discharged on exclusive feeding with breast milk.

RESULTS

A total of 87,381 pregnant women were prescreened for participation in the study, and a total of 77,220 mothers and 79,850 infants were screened for eligibility between November 30, 2017, and January 20, 2020; 5357 infants from 4859 mothers met the weight criteria for enrollment. Among them, 2944 mothers and 3211 infants underwent randomization, with 1470 mothers and 1609 infants assigned to immediate kangaroo mother care and 1474 mothers and 1602 infants assigned to conventional care, including kangaroo mother care after stabilization (Fig. 1).

Table 1 and Table S2 show the baseline characteristics of the infants and mothers in the study population as well as those of their families. Sociodemographic, newborn, and maternal characteristics were similar in the two groups. The mean gestational age at birth was 32.6 weeks and the mean birth weight 1.5 kg in both groups. With the exception of information on family income, which was missing for 8% of infants, observations for covariates were missing for only 0.3% of infants.

The median time to initiation of skin-to-skin contact in the intervention group was 1.3 hours (interquartile range, 0.8 to 2.7) and that in the control group was 53.6 hours (interquartile range, 33.8 to 101.4). The median duration of NICU stay was 6.4 days in both groups. During the NICU stay, the median daily duration of skin-to-skin contact in the intervention group was 16.9 hours and that in the control group was 1.5 hours. The daily duration of skin-to-skin contact on each day in the first 2 weeks is shown in Table S3. The main reasons that skin-to-skin contact was interrupted in infants in the intervention group were medical procedures, infant

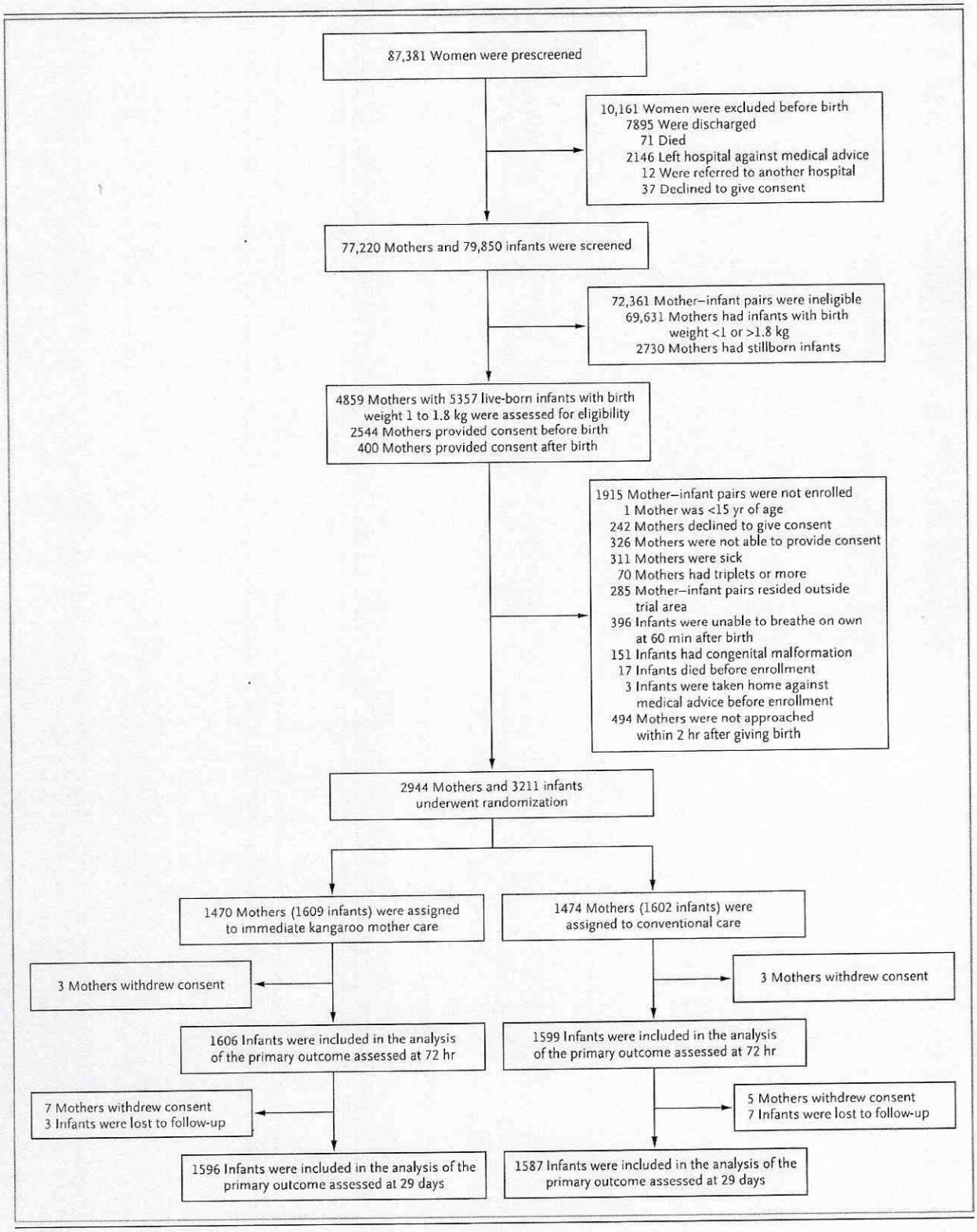
87,381 Women were prescreened
10,161 Women were excluded before birth
7895 Were discharged
71 Died
2146 Left hospital against medical advice
12 Were referred to another hospital
37 Declined to give consent
77,220 Mothers and 79,850 infants were screened
72,361 Mother–infant pairs were ineligible
69,631 Mothers had infants with birth weight <1 or >1.8 kg
2730 Mothers had stillborn infants
4859 Mothers with 5357 live-born infants with birth weight 1 to 1.8 kg were assessed for eligibility
2544 Mothers provided consent before birth
400 Mothers provided consent after birth
1915 Mother–infant pairs were not enrolled
1 Mother was <15 yr of age
242 Mothers declined to give consent
326 Mothers were not able to provide consent
311 Mothers were sick
70 Mothers had triplets or more
285 Mother–infant pairs resided outside trial area
396 Infants were unable to breathe on own at 60 min after birth
151 Infants had congenital malformation
17 Infants died before enrollment
3 Infants were taken home against medical advice before enrollment
494 Mothers were not approached within 2 hr after giving birth
2944 Mothers and 3211 infants underwent randomization
1470 Mothers (1609 infants) were assigned to immediate kangaroo mother care
1474 Mothers (1602 infants) were assigned to conventional care
3 Mothers withdrew consent
3 Mothers withdrew consent
1606 Infants were included in the analysis of the primary outcome assessed at 72 hr
1599 Infants were included in the analysis of the primary outcome assessed at 72 hr
7 Mothers withdrew consent
3 Infants were lost to follow-up
5 Mothers withdrew consent
7 Infants were lost to follow-up
1596 Infants were included in the analysis of the primary outcome assessed at 29 days
1587 Infants were included in the analysis of the primary outcome assessed at 29 days

Figure 1 (facing page). **Screening, Randomization, and Care.** There may have been more than one reason that a mother–infant pair was not enrolled in the trial.

care, and routine activities of the mother. The median daily duration of skin-to-skin contact in the kangaroo mother care ward was similar in the intervention and control groups (20.2 hours and 19.0 hours, respectively) (Table 2).

From enrollment to 28 days of age, 191 infants (12.0%) in the intervention group and 249 infants (15.7%) in the control group died (risk ratio, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P=0.001). The number needed to treat to prevent one death was 27 (95% CI, 17 to 77). From enrollment to 72 hours of age, 74 infants (4.6%) in the intervention group and 92 infants (5.8%) in the control group died (risk ratio for death, 0.77; 95% CI, 0.58 to 1.04; P=0.09) (Table 3).

The intervention had similar effects across the categories of birth weight, gestational age,

Table 1. **Baseline Characteristics of the Infants and Mothers and Their Households.***

Characteristic	Intervention	Control
Total no. of mother–infant pairs	1609	1602
Infants		
Median age at enrollment (IQR) — min	35 (20–55)	33 (20–54)
Mean birth weight — kg	1.5±0.2	1.5±0.2
Mean gestational age at birth — wk†	32.6±3.0	32.6±2.8
Male — no. (%)	752 (46.7)	748 (46.7)
Infants born as twins — no. (%)	430 (26.7)	430 (26.8)
Delivery by cesarean section — no. (%)	559 (34.7)	614 (38.3)
Site of birth — no. (%)		
Ghana	205 (12.7)	205 (12.8)
India	695 (43.2)	682 (42.6)
Malawi	217 (13.5)	222 (13.9)
Nigeria	108 (6.7)	107 (6.7)
Tanzania	384 (23.9)	386 (24.1)
Mother and household		
Total no. of mothers	1470	1474
Age of mother — yr	26.7±5.8	26.7±5.8
Median yr of schooling (IQR)‡	10 (7–12)	10 (7–12)
Monthly family income in U.S. dollars — median (IQR)	168 (110–285)	176 (110–280)
Piped water as main source of drinking water — no. (%)	934 (63.5)	953 (64.7)
Households with indoor toilet — no./total no. (%)	1288/1465 (87.9)	1343/1471 (91.3)

* Plus–minus values are means±SD. A total of 534 infants of 267 mothers were born from multiple pregnancies. All these infants were eligible for inclusion in the study and were enrolled, with 278 infants assigned to the intervention group and 256 infants assigned to the control group. In addition, there were 325 mothers with multiple pregnancies in whom only one of the infants was eligible for inclusion in the study (152 infants in the intervention group and 173 infants in the control group). IQR denotes interquartile range. Additional baseline characteristics are provided in Table S1 in the Supplementary Appendix.

† Gestational age was based on ultrasonographic findings in the first or second trimester. If such data were not available, gestational age was based on the mother's last menstrual period. If such data were not available, gestational age was based on Ballard score, which is determined on the basis of the neonate's physical and neuromuscular maturity.[13] Information on gestational age at birth was missing for 27 infants in the intervention group and 18 infants in the control group.

‡ Data on the mother's education were missing for two mothers in the intervention group and two mothers in the control group.

Table 2. **Initiation and Duration of Skin-to-Skin Contact of Infants with Mothers or Surrogates.***

Variable	Intervention (N=1609)	Control (N=1602)
Median time to initiation of skin-to-skin contact (IQR) — hr*	1.3 (0.8–2.7)	53.6 (33.8–101.4)
Time to initiation of skin-to-skin contact by category — no. (%)		
<2 hr	1084 (67.4)	4 (0.2)
2 to <6 hr	314 (19.5)	14 (0.9)
6 to <12 hr	94 (5.8)	13 (0.8)
12 to <24 hr	65 (4.0)	75 (4.7)
24 to <168 hr	35 (2.2)	1176 (73.4)
≥168 hr to end of neonatal period	1 (0.1)	142 (8.9)
Never initiated	16 (1.0)	178 (11.1)
Median duration of skin-to-skin contact in control NICU or Mother–NICU (IQR) — hr/day	16.9 (13.0–19.7)	1.5 (0.3–3.3)
With mother	12.3 (6.8–16.5)	1.5 (0.2–3.2)
With surrogate	2.3 (0.1–6.5)	0 (0–0)
Duration of skin-to-skin contact in kangaroo mother care ward — hr/day		
Total no. of hr	1300	1224
Median (IQR) — hr/day	20.2 (18.6–21.3)	19.0 (16.3–20.4)
With mother	19.4 (14.8–20.6)	18.0 (14.1–19.9)
With surrogate	0 (0–0.85)	0 (0–0)

* If skin-to-skin contact was never initiated and the infant died, the data were censored at the time of death; if the infant was taken home against medical advice or if the mother refused to provide consent, the data were censored at time that the mother and infant left the hospital or at the time that consent was refused; if the mother and infant were discharged during the study, the data were censored at time of discharge; if the mother and the infant remained in the hospital at the end of the neonatal period, the data were censored at day 28.

weight for gestational age, type of delivery, and singletons or twins (Fig. 2 and Fig. S1). Benefit in point estimates was reported at all sites except Ghana. In the intervention group, the risk of death was lower in infants who received more hours of skin-to-skin contact per day (Table S4). Most deaths were caused by sepsis or preterm birth complications. Sepsis-associated mortality was 4.4% in the intervention group and 6.9% in the control group (risk ratio for death, 0.64; 95% CI, 0.48 to 0.86) (Table S5). Among 2146 infants with a birth weight of between 1.0 and 1.799 kg who were not enrolled in the trial, 340 (15.8%) had died by 72 hours.

Results for secondary outcomes are shown in Table 3. The proportion of infants with suspected sepsis was 22.9% in the intervention group and 27.8% in the control group (adjusted risk ratio, 0.82; 95% CI, 0.73 to 0.93); hypothermia was documented in 5.6% and 8.3% of infants, respectively (adjusted risk ratio, 0.65; 95% CI, 0.51 to 0.83). The time to stabilization and the incidence of hypoglycemia, feeding fully by suckling at the time of discharge, and exclusive breast-feeding at the end of the neonatal period were similar in both groups. In post-hoc analyses, breast-feeding was initiated within the first 24 hours after birth in 58.5% of infants in the intervention group and 45.5% of infants in the control group; full breast-feeding occurred within 7 days in 78.4% and 69.0% of infants, respectively (Table S6).

DISCUSSION

In this multicenter trial, the initiation of continuous kangaroo mother care soon after birth in infants with a birth weight between 1.0 and 1.799 kg improved neonatal survival by 25% as compared with kangaroo mother care initiated

Table 3. Primary and Secondary Outcomes.*

Outcome	Intervention (N=1609)	Control (N=1602)	Risk Ratio, Hazard Ratio, or Difference (95% CI)†	P Value
Primary				
Death between enrollment and 28 days — no./total no. (%)	191/1596 (12.0)	249/1587 (15.7)	0.75 (0.64–0.89)	0.001
Death between enrollment and 72 hr after birth — no./total no. (%)	74/1606 (4.6)	92/1599 (5.8)	0.77 (0.58–1.04)	0.09
Secondary‡				
Exclusive breast-feeding at end of neonatal period — no./total no. (%)	1208/1401 (86.2)	1140/1336 (85.3)	1.01 (0.98–1.05)	
Fully breast-fed (i.e., by suckling) at hospital discharge — no./total no. (%)	62/1435 (4.3)	55/1376 (4.0)	1.06 (0.73–1.53)	
Hypothermia — no./total no. (%)§	90/1609 (5.6)	133/1602 (8.3)	0.65 (0.51–0.83)	
Median time to clinical stabilization — hr (IQR)¶	73.8 (26.8–138.5)	74.8 (25.3–140.6)	0.98 (0.90–1.07)‖	
Suspected sepsis — no./total no. (%)**	361/1575 (22.9)	434/1561 (27.8)	0.82 (0.73–0.93)	
Hypoglycemia at any time between 0 and 36 hr after birth — no./total no. (%)††	82/799 (10.3)	66/651 (10.1)	1.15 (0.85–1.56)	
Mean duration of hospital stay — days‡‡	14.9±0.2	15.2±0.2	1.07 (0.99–1.16)‖	
Mean score for maternal satisfaction§§	9.2±1.0	9.1±1.2	0.11 (0.03–0.19)¶¶	
Maternal depression — no./total no. (%)‖‖	2/1276 (0.2)	7/1231 (0.6)	0.23 (0.05–1.14)	

* Plus–minus values are means ±SD.

† All the values are adjusted risk ratios, except where noted. Risk ratios were adjusted for clustering due to multiple births and in accordance with study site, type of delivery, multiple pregnancies, mother's age at randomization, infant's sex and weight, mother's years of schooling and age, household with toilet, and family income.

‡ The 95% confidence intervals for secondary outcomes were not adjusted for multiplicity and should not be used to infer definitive intervention effects.

§ Hypothermia was defined as any instance of an axillary temperature of less than 36°C at any time from 2 hours after randomization until hospital discharge.

¶ The time to clinical stabilization was defined as the first time at which an infant had all signs of clinical stability (i.e., no need for continuous positive airway pressure therapy, no episodes of apnea, an oxygen saturation of more than 90%, a respiratory rate of 40 to 59 breaths per minute, a heart rate of 80 to 179 beats per minute, a temperature of 36.0 to 37.4°C, and no need for intravenous fluids).

‖ This value is the hazard ratio with a 95% confidence interval.

** Suspected sepsis was defined as one or more of the following signs or symptoms: temperature of 35.5°C or more than 38°C, no movement or movement only on stimulation, in-drawing of the chest, and convulsions. Signs and symptoms were not reported for the first 24 hours of life. After that time, the infant should have been well for at least 24 hours before becoming sick. The denominator excludes infants who died, whose parents took them home against medical advice, or who were discharged before reaching 48 hours of age.

†† Hypoglycemia was defined as a blood glucose level of less than 45 mg per deciliter (2.5 mmol per liter), measured when clinically indicated.

‡‡ The duration of hospital stay was a prespecified process outcome.

§§ The score for maternal satisfaction with health care in the hospital was assessed at discharge in 1282 mothers in the intervention group and 1233 mothers in the control group on a scale of 1 to 10, with higher scores indicating greater satisfaction.

¶¶ This value is the mean difference with a 95% confidence interval.

‖‖ Maternal depression was defined as a score of 15 points or more on the PHQ-9 Patient Depression Questionnaire. On this questionnaire, scores of 0 to 4 indicate no depression, 5 to 9 mild depression, 10 to 14 moderate depression, 15 to 19 moderately severe depression, and 20 to 27 severe depression.

Subgroup	Intervention	Control	Risk Ratio for Death at 28 Days (95% CI)
	no. of deaths/total no. (%)		
Birth weight			
1.0 to <1.2 kg	47/163 (28.8)	62/179 (34.6)	0.84 (0.63–1.13)
1.2 to <1.5 kg	83/537 (15.5)	102/517 (19.7)	0.78 (0.60–1.02)
1.5 to <1.8 kg	61/896 (6.8)	85/891 (9.5)	0.72 (0.52–0.98)
Gestational age			
<31 wk	74/354 (20.9)	94/333 (28.2)	0.78 (0.59–1.02)
31 to <34 wk	57/638 (8.9)	84/690 (12.2)	0.72 (0.52–0.98)
34 to <37 wk	29/440 (6.6)	46/418 (11.0)	0.60 (0.38–0.93)
≥37 wk	9/138 (6.5)	13/128 (10.2)	0.58 (0.25–1.35)
Type of delivery			
Vaginal birth	132/1037 (12.7)	166/977 (17.0)	0.75 (0.61–0.93)
Cesarean section	59/559 (10.6)	83/610 (13.6)	0.78 (0.57–1.07)
Singleton or twins			
Singleton	153/1170 (13.1)	195/1162 (16.8)	0.78 (0.64–0.94)
Twins	38/426 (8.9)	54/425 (12.7)	0. 70 (0.46–1.05)
Size for gestational age			
Small	55/634 (8.7)	72/613 (11.8)	0.73 (0.52–1.02)
Not small	113/935 (12.1)	165/956 (17.3)	0.70 (0.56–0.88)
Site			
Ghana	25/205 (12.2)	22/204 (10.8)	1.13 (0.66–1.95)
India	69/692 (10.0)	102/680 (15.0)	0.66 (0.50–0.89)
Malawi	38/212 (17.9)	50/212 (23.6)	0.76 (0.52–1.12)
Nigeria	11/108 (10.2)	13/107 (12.2)	0.84 (0.39–1.79)
Tanzania	48/379 (12.7)	62/384 (16.2)	0.78 (0.55–1.12)

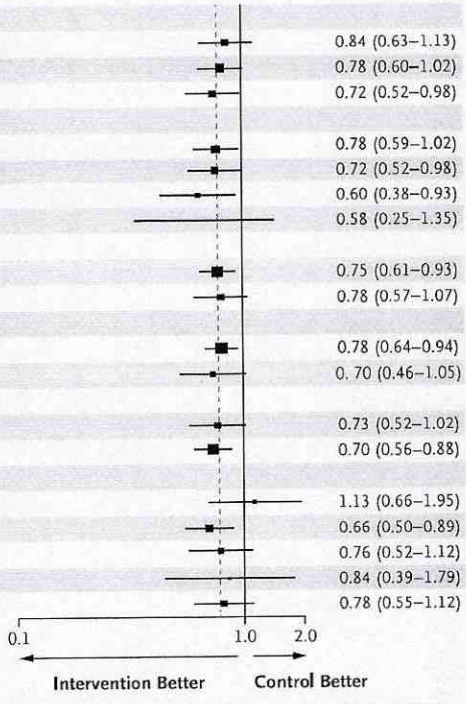

Figure 2. Subgroup Analyses of Mortality.

There were 26 infants in the intervention group and 18 infants in the control group for whom information on gestational age at birth was missing. Size for gestational age could not be calculated for one additional infant. The risk ratio was adjusted according to study site and clustering owing to multiple births. For the subgroup analysis by site, adjustment was made only for clustering owing to multiple births. Since the widths of the confidence intervals were not adjusted for multiplicity, the intervals should not be used to infer definitive intervention effects. The size of each square representing a point estimate is proportional to the weight assigned to the subgroup.

after stabilization, the approach that is currently recommended. In order to prevent one neonatal death, the intervention would have to be provided to 27 infants (95% CI, 17 to 77). Implementation of the intervention required the mother or a surrogate to be with the infant 24 hours a day for the duration of stay in the NICU, which required the establishment of Mother–NICUs. The lower observed rates of hypothermia and suspected sepsis, though not adjusted for multiplicity, are consistent with results for the primary outcome and may at least in part explain the lower mortality among the infants receiving immediate kangaroo mother care.

Findings for the primary outcome and for infection and hypothermia were similar to those reported in earlier trials of the use of kangaroo mother care in clinically stable infants.[6] However, we did not find significant differences between the intervention and control groups in the two prespecified feeding outcomes — being fully breast-fed by suckling at discharge and being fed exclusively through breast-feeding at the end of the neonatal period — despite post-hoc analyses suggesting that in the intervention group there were higher rates of initiating breast-feeding within 24 hours, putting the baby to the breast within 72 hours after birth, and reaching full breast-feeding within 7 days of birth. Nor did we find a material difference between groups in the time to stabilization, unlike two previous studies involving a similar intervention.[8,9] As compared with the studies that achieved intermittent kangaroo mother care in

the Cochrane review,[6] we achieved high compliance with the intervention — that is, approximately 17 hours of skin-to-skin contact per day.

There are several possible mechanisms by which immediate kangaroo mother care might confer benefit. Since the mother and baby are in close contact from birth, the baby is more likely to be colonized by the mother's protective microbiome and more likely to receive early breastfeeding. There is also less handling of the baby by other persons, thus reducing the risk of infection.[14-20] Constant monitoring of the infant by the mother, more frequent monitoring of the infant's glucose levels, and absence of stress[21] related to mother–infant separation may also have contributed to reduced mortality. Further studies in well-resourced settings could help to determine to what extent these enhanced survival results in low- and middle-income countries are relevant to settings in which mortality is low and intensive infant monitoring is provided. We observed that the risk of death was lower in infants who received more hours of skin-to-skin contact per day. However, this association is subject to confounding by medical issues in the infant that may have precluded prolonged skin-to-skin contact.

The results of the study are generalizable to most hospitals in low-resource settings in which immediate kangaroo mother care can be implemented as described here. Challenges in scaling up of the intervention include the involvement of multiple stakeholders, the establishment of Mother–NICUs, the need for strong collaboration between the obstetrics and neonatal departments, and changes in policy that would allow surrogates to provide kangaroo mother care.

Some limitations merit discussion. The nature of the intervention made blinding impossible. However, ensuring allocation concealment until the completion of enrollment, rigorous adherence to a predefined protocol, and the choice of mortality as a primary outcome minimize measurement bias. The open-label design may have resulted in measurement bias in some of the secondary outcomes, which were more subjective, but would not affect our primary outcomes regarding mortality. The heterogeneity in the infrastructure, staff, and practices and possible differences in patient profiles across sites should increase the generalizability of our findings. It is not possible to partition the beneficial effect of the intervention between immediate initiation of kangaroo mother care and the simple presence of the mother with her baby because both are integral parts of the intervention. Finally, approximately 20% of the infants weighing between 1.0 and 1.799 kg who were born in study hospitals were not enrolled because the mother or the newborn was determined to be too sick to participate; this limitation needs to be considered when estimating the potential public health effects of the intervention.

In this large, multisite, multicountry study conducted in low-resource hospitals, continuous kangaroo mother care initiated immediately after birth in infants with a birth weight between 1.0 and 1.799 kg resulted in a significantly lower risk of neonatal death than the currently recommended initiation of kangaroo mother care after stabilization.

This study was reviewed and approved by the World Health Organization Ethics Review Committee and the institutional review boards at the five study sites: the School of Medical Science–Komfo Anokye Teaching Hospital, Ghana; Vardhman Mahavir Medical College and Safdarjung Hospital, India; the Malawi College of Medicine, Malawi; the Obafemi Awolowo University Teaching Hospitals Complex, Nigeria; and the National Institute for Medical Research, Tanzania.

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APPENDIX

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