


STUDY PROTOCOL

Open Access



Evaluation of the impact of continuous Kangaroo Mother Care (KMC) initiated immediately after birth compared to KMC initiated after stabilization in newborns with birth weight 1.0 to < 1.8 kg on neurodevelopmental outcomes: Protocol for a follow-up study

E. A. Adejuyigbe¹, I. Agyeman², P. Anand³, H. C. Anyabolu¹, S. Arya³, E. N. Assenga⁴, S. Badhal⁵, N. W. Brobby⁶, H. K. Chellani^{3*}, N. Chopra³, P. K. Debata³, Q. Dube⁷, T. Dua⁸, L. Gadama⁹, R. Gera³, C. K. Hammond⁶, S. Jain⁵, F. Kantumbiza¹⁰, K. Kawaza¹⁰, E. N. Kija⁴, P. Lal¹¹, M. Mallewa¹⁰, M. K. Manu², A. Mehta⁵, T. Mhango¹⁰, H. E. Naburi⁴, S. Newton¹², I. Nyanor¹³, P. A. Nyako¹⁴, O. J. Oke¹, A. Patel^{8,15}, G. Phlange-Rhule¹⁶, R. Sehgal³, R. Singhal¹⁷, N. Wadhwa^{18*}  and A. B. Yiadom⁶

Abstract

Background Preterm birth or low birth weight is the single largest cause of death in newborns, however this mortality can be reduced through newborn care interventions, including Kangaroo Mother Care (KMC). Previously, a multi-country randomized controlled trial, coordinated by the World Health Organization (WHO), reported a significant survival advantage with initiation of continuous KMC immediately after birth compared with initiation of continuous KMC a few days after birth when the baby is considered clinically stable.

Whether the survival advantage would lead to higher rates of neurodevelopmental morbidities, or the immediate KMC will also have a beneficial effect on cognitive development also, has not been investigated. We therefore propose to test the hypothesis that low-birth-weight infants exposed to immediate KMC will have lower rates of neurodevelopmental impairment in comparison to traditional KMC-treated infants, by prospectively following up infants already enrolled in the immediate KMC trial for the first 2 years of life, and assessing their growth and neurodevelopment.

*Correspondence:

H. K. Chellani
chellaniharish@gmail.com
N. Wadhwa
nitya.wadhwa@thsti.res.in

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Methods This prospective cohort study will enroll surviving neonates from the main WHO immediate KMC trial. The main trial as well as this follow-up study are being conducted in five low- and middle-income countries in South Asia and sub-Saharan Africa. The estimated sample size for comparison of the risk of neurodevelopmental impairment is a total of 2200 children. The primary outcome will include rates of cerebral palsy, hearing impairment, vision impairment, mental and motor development, and epilepsy and will be assessed by the age of 3 years. The analysis will be by intention to treat.

Discussion Immediate KMC can potentially reduce low-birth-weight-associated complications such as respiratory disease, hypothermia, hypoglycemia, and infection that can result in impaired neurocognitive development. Neuroprotection may also be mediated by improved physiological stabilization that may lead to better maturation of neural pathways, reduced risk of hypoxia, positive parental impact, improved sleep cycles, and improved stress responses. The present study will help in evaluating the overall impact of KMC by investigating the long-term effect on neurodevelopmental impairment in the survivors.

Trial registration Clinical Trials Registry-India CTRI/2019/11/021899. Registered on 06 November 2019.

Trials registration of parent trial: ACTRN12618001880235; Clinical Trials Registry-India: CTRI/2018/08/015369.

Keywords Immediate Kangaroo Mother Care (iKMC), Low-birth-weight babies, Neurodevelopment, Low- and middle-income countries

Background

Nearly, 15.5% of all births, or more than 20 million infants worldwide, are born with low birth weight (LBW) as a result of preterm birth or intrauterine growth restriction or both [1, 2]. Preterm birth or LBW is the single largest cause of death in newborns, but the mortality can be reduced by effective newborn care interventions. However, for years, it was demonstrated that although mortality was being improved by interventions for LBW newborns, the impact on morbidity, including neurocognitive impairment and motor disabilities, was unchanged [3]. More recently, there is evidence suggesting that infant survival with improved neurodevelopmental outcomes is increasing slightly and is associated with both improved medical interventions and maternal factors [4]. However, there is also a concern of an increased risk of neurodevelopmental impairment, and this enigma needs to be addressed by a systematic study. Therefore, while evaluating the impact of any intervention on mortality in this population, it is equally important to study the risk of neurodevelopment impairments, including cerebral palsy, hearing and vision impairment, cognitive impairment, and epilepsy.

The World Health Organization (WHO) defines Kangaroo Mother Care (KMC) as a technique used in preterm and LBW infants of continuous skin-to-skin contact between mother and baby until the infant shows signs of intolerance. Exclusive breastfeeding is also encouraged as an essential component of KMC. Notably, however, it is currently recommended that continuous KMC should be initiated only once the baby is stable, meaning that the baby must be breathing spontaneously without additional oxygen [5].

“WHO recommendations on interventions to improve preterm birth outcomes” recommends KMC for the routine care of newborns weighing 2.0 kg or less at birth, which should be initiated in health care facilities as soon as the newborns are clinically stable [6]. These babies should be provided as close to continuous KMC as possible. Intermittent KMC, rather than conventional care, is recommended for newborns weighing 2.0 kg or less at birth, if continuous KMC is not possible [6]. There is no current recommendation for KMC for unstable <2.0 kg neonates. A recently updated Cochrane review reported 40% lower mortality in infants with birth weight <2.0 kg given KMC compared to mortality in those who were given standard care in hospitals, at 40 to 41 weeks post-menstrual age [7]. In almost all studies included in the Cochrane review, KMC was initiated after the baby was clinically stable, with the median age at initiation of KMC 3.2 to 24.5 days [7]. Two randomized controlled trials (RCTs) comparing immediate versus conventional KMC from South Africa and Vietnam [8–10] showed favorable results for immediate KMC initiation. This data led the World Health Organization to coordinate a multi-country randomized controlled trial to evaluate the effect of initiating continuous KMC immediately after birth on survival (compared with initiation of continuous KMC a few days after birth when the baby is considered clinically stable). This RCT assessed newborn survival outcomes over the acute hospital period up to a 28-day follow-up [11]. The study enrolled 3211 infant-mother dyads with 1609 dyads in the intervention arm and 1602 in the control arm. The median daily duration (hours) of skin-to-skin contact was 16.9 h (IQR 13.0–19.7) in the intervention and 1.5 h (IQR 0.3–3.3) in the control arm.

Neonatal death occurred in 12.0% and 15.7% infants, respectively, in the two arms (RR 0.75; 95% CI 0.64–0.89; $p=0.001$). The study concluded that in infants with birth weight between 1.0 and <1.8 kg, immediate KMC (versus conventional KMC care) resulted in a significant reduction in neonatal mortality [12]. However, in order to evaluate the overall impact of KMC, the long-term effect on neurodevelopment in the survivors should be assessed.

It has been observed that KMC can reduce bradycardia and oxygen desaturation events in preterm infants, providing physiological stability and possible benefits for neurodevelopmental outcomes [13]. Few studies involving KMC initiated in stable infants show that KMC has a beneficial effect on both short-term [14] and long-term [15, 16] neurodevelopmental outcomes of preterm and LBW babies compared to no KMC. The long-lasting social and behavioral protective effects have been observed beyond 20 years after the KMC intervention [17].

Studies have suggested that there is a positive impact of KMC on parental interaction due to not only increased skin-to-skin contact but also increased opportunity for bonding through breastfeeding and, as a result, impact on the child's behavior, which can be long lasting. However, the degree of direct impact on cognition, language, motor, auditory, and vision impairment has not been consistent, although most studies do demonstrate a positive trend in these domains [17–21]. Furthermore, emerging evidence from smaller studies suggests that, in addition to the positive parental impact, the implementation of KMC may also be neuroprotective through both improved sleep cycles and brain maturation patterns seen on EEG [22, 23], as well as improved stress responses in general, which had a lasting impact when reviewed over a 10-year period on both emotional and cognitive development [24].

Despite the evidence of the benefit of KMC after stabilization on neurodevelopmental outcomes, an evaluation of the long-term effects of the KMC initiated immediately after birth on the risk of neurodevelopmental impairment such as motor or sensory impairment or cognitive deficits is not well known.

We hypothesize that KMC initiated immediately after birth can improve physiological stabilization and potentially lead to anatomical or functional changes in the brain in the neonatal period, thus allowing for better maturation of the brain and pathways leading to a possible decrease in neurocognitive morbidity as well as reduce the risk of hypoxia, thus decreasing long-term morbidity. In addition, given the positive impact of traditional KMC on parental bonding, it is argued that the earlier KMC is initiated (e.g., with immediate KMC), the stronger the bond, leading to better family

motivation and stimulation and thus positively impacting on child development.

The main outcome of interest for the parent study on immediate KMC was the impact on neonatal mortality [11, 12]. Evidence of the longer-term effect of the intervention on the risk of neurodevelopmental impairment, growth, and mortality beyond the neonatal period, on the other hand, will provide additional evidence and rationale for policy change as the intervention targets survival as well as helping babies to thrive.

We therefore propose to follow up the newborns enrolled in the recently published immediate KMC study [11, 12], beyond the neonatal period up to 3 years of age to additionally study the risk of neurodevelopmental impairments, specifically the risk on growth, feeding, caregiving practices, mortality, and home environment. Our main hypothesis is that those newborns who were provided continuous KMC initiated immediately after birth will experience a reduced risk of neurodevelopmental impairment, including the risk of cerebral palsy, hearing impairment, vision impairment, mental and motor impairments, and epilepsy, compared with a similar group in whom KMC was initiated only after stabilization.

Methods

Study design

This is a prospective cohort study of the children already enrolled in the immediate KMC randomized controlled trial to evaluate the impact of continuous Kangaroo Mother Care initiated immediately after birth (iKMC) on survival of newborns with birth weight between 1.0 and <1.8 kg [11, 12].

Study setting

As this study is a follow-up of the concluded and recently published iKMC trial [12], the study is being conducted at the same five LMIC study sites encompassing hospitals in Ghana, India, Malawi, Nigeria, and Tanzania. The selected facilities are tertiary care hospitals that care for small and sick newborns with a high proportion of LBW babies and follow-up high-risk newborns. As part of standardization across the involved study sites, prior to the study, trainings and standardization assessments were done to ensure all participating sites could offer the WHO minimum package of care for small and sick newborns [11].

Study population

All infants born with birth weight between 1.0 and <1.8 kg, enrolled in the main trial, who survive the

neonatal period, and whose parents consent for their participation in the follow-up study, are eligible to be enrolled.

All infants who die within the first month of life or whose parents refuse consent for follow-up will be excluded from the study.

We employ two strategies to approach the parents for enrolment. First, we approach the mother/parent during the 29-day follow-up visit for the main trial. The second strategy is for children who have completed the 29-day follow-up visit in the main trial. For these children, we approach the mother/parent either telephonically or when they visit the high-risk infant follow-up clinic as part of standard hospital care. A verbal preconsent is taken and an in-person hospital visit is scheduled for a detailed written informed consent for participation in the follow-up study.

Sample size calculation

The sample size for the main iKMC trial was a total of 4200 neonates. Early completion in January 2020 led to a total of 3211 neonates being enrolled in the main iKMC trial. A preliminary review of literature of neurodevelopment in infants between 1 and < 1.8 kg shows the prevalence of any of the conditions of cerebral palsy, hearing impairment, vision impairment, and mean development scores to vary from 5 to 25% [25–27]. Any neurodevelopmental impairment (e.g., cerebral palsy, Bayley score < 85, hearing or vision impairment) in the study population is estimated to be approximately at 15–25%. We estimated the sample size for comparison of the risk of neurodevelopmental impairment in control and intervention groups (20% compared with 15% or 25% [25% lower or higher]) with 80% power and a significance level of 5% to be 1100 per group, requiring a total of about 2200 children.

We thus propose to enroll 2200 babies from the main trial to reach the above-mentioned sample size.

The intervention

The proposed study is a follow-up of the already concluded randomized controlled trial for evaluating the effect of immediate KMC on infant survival. The intervention and control groups were assigned during the main iKMC trial where KMC is defined as continuous skin-to-skin contact with 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.

In the intervention group, the mother and baby remained in skin-to-skin contact from the time of randomization whereas the newborns randomized to

the control group received conventional care, and the mother and baby were separated until the baby was clinically stable. The details of intervention and control arms and care of the newborns in both the groups are described in the already published protocol paper [11].

Care of children in both intervention and control groups for the follow-up study

For the ongoing follow-up study, care of the children continues to be as per each site's routine policy and standard of care, including routine health monitoring visits, care for acute illnesses, and management of morbidities including neurodevelopment impairments. This includes appropriate early diagnosis and management of the neurodevelopmental outcomes of interest. Children with suspicion of epilepsy are referred to appropriate neurologic or child health services for confirmation and management according to national protocols. Those with motor impairments are referred to local rehabilitation specialists for physical therapy as per local resource availability. For any child with signs of developmental impairment (motor, cognitive, or social-behavioral), referral to appropriate early stimulation programs is provided. Early monitoring for vision and hearing impairment is performed routinely and in case of any suspicion, the children are referred to appropriate ophthalmologic and audiology or otolaryngology specialists for appropriate management and to adapt to environment. For every child that has been identified as having neurodevelopmental impairment, each site in line with their standard protocol for the identification, assessment, management, and follow-up care develops an individual care plan (including rehabilitation, psychosocial support, etc.) in consultation with the child's parents.

Primary and secondary outcomes

The primary outcome of the follow-up study is the presence of neurodevelopmental impairments assessed by the age of 3 years in all enrolled children. The study duration and window for the last outcome assessment were extended from 2 to 3 years after ethics approval, due to the COVID-19 pandemic. Specifically, this composite outcome includes rates of motor impairment and risk of cerebral palsy, hearing impairment, vision impairment, cognitive, language, motor, socio-emotional or adaptive behavior, and epilepsy and the presence of any one or more will be considered as neurodevelopmental impairment. Secondary outcomes include growth and feeding practices, mortality and home environment (maternal depression and parent-child interactions), and rates of overnight hospital admissions.

Outcomes are assessed via standardized tools and questionnaires (Table 1). Motor impairment and risk of cerebral palsy are measured by standardized neurologic evaluation, using a validated tool, Hammersmith Infant Neurological Examination (HINE) at 6 months, 1 year, and 2 years of age. Cognitive, language, motor, socio-emotional, or adaptive behavior is assessed using Bayley Scales of Infant and Toddler Development (BSID III) at 2 to 3 years of age. Epilepsy is diagnosed using a standardized questionnaire, with operationalization of the International League against Epilepsy (ILAE) definition. Hearing is evaluated at discharge from the hospital or as soon as possible after enrolment in the follow-up study. First, an assessment by screening auditory brainstem responses (ABR) is performed at the facility. If the infant clears this assessment, no further assessment for hearing is required. In case the infant fails this initial screening, he/ she is referred to the audiologist or specialist for re-screening including a diagnostic ABR if required. Visual acuity is measured using Teller Acuity Cards, at or any time after 1 year of age at the facility.

The schedule of outcome assessments is shown in Table 2. As this is a follow-up study of the main iKMC trial participants, and was initiated in a phased manner in January 2019, approximately 14 months after the start of the parent trial, infants are enrolled on a rolling basis. While all efforts are made to recruit the infant within the first 3 months, participants from the parent trial who have completed 3 months of age prior to the follow-up study start date are recruited after the initial assessment time points. Assessments for outcome measurements are performed at the earliest age-appropriate time point feasible for the individual child upon enrolment for this follow-up study. Due to the challenge posed by the COVID-19 pandemic with ensuing lockdowns and permanent movement of many of the children of migrant laborers to distant areas, the age window for enrolment and completion of all assessments was extended to 36 months, and we switched to telephonic follow-up wherever we could but retained in-person follow-up for the primary outcome measurement at 12 and 24–36 months. This was implemented after due approval from the institutional review boards (IRBs) or ethics committees.

Blinding

While the main iKMC trial evaluating the impact on newborn survival did not incorporate blinding due to the nature of the intervention, during the follow-up assessments, evaluators conducting the standardized assessments are blinded to whether the child received the intervention or not to decrease the bias.

Study implementation strategy

The iKMC follow-up study is being conducted in a standardized manner across all the sites in the five countries. Each site has constituted dedicated multidisciplinary teams to perform the different activities—study conduct, internal quality control, project management, and data management. The conduct team responsible for consent as well as follow-up of the enrolled children for outcome measurements comprises research assistants, clinical psychologist, audiologist, and field workers. The investigators who are clinicians are responsible for overall study conduct and quality assurance and quality control. Each team member is trained in the protocol, Good Clinical Practice (GCP), and study-specific standard operating procedures specific to their role and responsibility. A site coordinator is responsible for coordinating the implementation of the follow-up study at each site. A central team led by WHO headquarters coordinates the conduct across all sites, ensures harmonization of processes, and monitors quality and study progress.

Infrastructure

An important fallout of the study has been infrastructure development. Each site has developed a designated child development assessment unit. The unit has separate designated areas for registration and screening, consent, anthropometry, structured neurological assessment using HINE, developmental assessment using BSID III, visual acuity using Teller Acuity Cards, hearing assessment using auditory brainstem responses, and data entry and management.

Enrolment and outcome measurements

The study conduct research staff is responsible for consent as well as follow-up of the enrolled children for outcome measurements.

They are blinded to the intervention or control group allocation of enrolled children as they were not involved with intervention delivery during the main trial conduct. The staff performing outcome assessments had an initial intensive training on the standardized and validated tools being used for assessing primary and secondary outcomes of the follow-up study described in Table 1. For any identified neurodevelopmental impairment, an appropriate standard of care management is provided to the child.

Quality assurance and quality control

The study has a well-structured quality assurance plan that is being implemented at all sites. The site coordinators ensure adherence to the manual of operations. The study has employed several checks to ensure the quality of all aspects of the follow-up study including the consent

Table 1 Outcome measurements

Outcomes	Tool	Measurement strategy	Rationale
<p>Primary outcome</p> <p>Developmental delay</p>	<p>Bayley Scales of Infant and Toddler Development III (BSID III)</p> <p>The scale is used to assess language, cognitive, motor, social-emotional, and general adaptive functions</p>	<p>Assessment by Bayley-trained clinical psychologist/clinician between 24-and-36-month chronological age</p> <p>The BSID III scores will be calculated using corrected gestational age</p> <p>For the BSID III, the composite score range in different domains is as follows:</p> <p>Cognitive: 55–145</p> <p>Language: 47–153</p> <p>Motor: 46–154</p> <p>Social-emotional: 55–145</p> <p>Adaptive: 40–160</p> <p>Composite score in each individual domain may be converted into scaled scores that range from 1 to 19. Average scaled scores are between 8 and 12</p> <p>A composite score of < 80 will indicate developmental delay</p>	<p>BSID III has been developed in the USA and used in LMIC countries, including India [28–31]</p> <p>BSID III, in comparison to BSID II, requires a higher cutoff score for comparable sensitivity in detecting developmental delay. BSID III combined scores < 80 and cognitive and language scores < 85 were found to correlate with BSID II Mental Development Index (MDI) scores < 70 and clinically to moderate-severe developmental delay [31]</p>
Cerebral palsy	Hammersmith Infant Neurological Examination (HINE)	<p>Standardized neurological assessment using HINE at 6, 12, and 24 months</p> <p>According to a recent systematic review [32], HINE scores have 90% predictive accuracy of cerebral palsy</p> <p>By 12 months, a score of < 40 is predictive of non-ambulatory cerebral palsy [plegic, not walking] and a score of 40–60 is predictive of ambulatory cerebral palsy [able to walk], with any score < 70 considered abnormal. The maximum score is 78</p> <p>The accepted norms will be used for the cutoff in this study, which are > 70 at 6 months and > 73 at 12 months and older [32–37]</p> <p>Due to the risk of more subtle findings, particularly in premature infants, there is increased sensitivity to the tool when used at multiple time points; therefore, the examination will be performed at an additional time point of 2 years</p> <p>For the primary outcome, the score at the 12- and 24-month assessments will be considered</p>	<p>HINE is a strongly recommended scale for early diagnosis of cerebral palsy [32]</p> <p>It is a standardized and scorable clinical neurological examination that is applicable for infants aged between 2 and 24 months and has been shown to be an easy-to-train tool with interobserver reliability even in less experienced staff [38]</p>
Hearing impairment	Hearing assessment measured ideally at discharge or as soon as possible at enrolment or first follow-up	<p>First assessment by screening auditory brainstem responses (ABR)</p> <p>If screening ABR is passed, no need for further hearing assessment tests</p> <p>In case screening ABR is failed, the participant is referred at the earliest possible opportunity to audiologist or specialist for re-screening, including diagnostic ABR as applicable. Hearing impairment is defined as failed diagnostic ABR or failed re-screening ABR if diagnostic ABR is not available</p>	<p>International guidelines recommend hearing assessment within the first month of life whenever feasible [39]</p> <p>While Otoacoustic Emission (OAE) screening can be used in settings where ABR is not available, it is less preferred due to the potential for missing retro-cochlear hearing loss. Therefore, in studying high-risk infants, ABR is preferred [39–42]</p>

Table 1 (continued)

Outcomes	Tool	Measurement strategy	Rationale
Vision impairment	Structural visual examinations, including for retinopathy of prematurity, will be performed between discharge and 3 months, with visual acuity measured at 12 months	Visual acuity measured by Teller Acuity Cards at the facility Impairment defined by measurements 2 lines less than age-defined normative values	Teller Acuity Cards will be used due to the availability of age-specific reference ranges [43, 44]
Epilepsy	Screen for seizure at each follow-up visit. If screening positive, refer to a clinician	First assessment by epilepsy screening questionnaire at each follow-up visit If the participant screen negative, there is no need for further assessment tests In case the participant is screened positive, he/she will be assessed by a pediatrician/pediatric neurologist by a diagnostic questionnaire to arrive at a diagnosis of epilepsy/no epilepsy using the ILAE definition [45]. To reduce variability in diagnosis for purposes of this study, the ILAE diagnostic criterion has been operationalized for this study in the diagnostic questionnaire as either 2 unprovoked seizures separated by at least 24 h or 1 unprovoked seizure and one other positive finding of neurodevelopmental impairment	Screening questionnaires for pediatric epilepsy are limited due to small populations and limited age range and have demonstrated moderate validity [46, 47] A questionnaire comprised from validated pediatric epilepsy screening questionnaires and agreed upon by pediatric neurologists from the participating sites has been employed after local pilot testing
Secondary outcomes			
Mortality	Screen for death of enrolled child occurring any time between 29 days and 3 years of age	Mortality/survival status at each screening point. Assessments performed every 3 months until the age of 3 years	
Growth	Anthropometric parameters of weight (W), length (L), and head circumference (HC) for age using standardized equipment	Anthropometry at 6, 12, and 24 months of age. Parameters are plotted as per corrected age on WHO Multicentre Growth Reference Study (MGRS) charts and interpreted as per z scores Postnatal growth failure defined as fall in z scores or z scores < 2 SD	Measurements are obtained during facility visits. In case the participant is unable to visit the facility, we perform the measurement at the home of the participant
Feeding practices	Assessment of breastfeeding, expressed breast feeds, complementary feeds at 6 months, and adequacy of feeding beyond infancy	Feeding practices measured through a standard questionnaire at each follow-up visit—every 3 months until the age of 3 years	
Maternal depression	Patient Health Questionnaire 9 (PHQ-9)	Maternal depression measured using PHQ-9 at 6 and 12 months of age	Literature suggests, while early screening for post-partum depression is important, additional screening points at either 6 or 12 months can capture additional women who may have initially screened negative at earlier time points. Therefore, we have included these time points in this study [48]

Table 1 (continued)

Outcomes	Tool	Measurement strategy	Rationale
Home environment	HOME	Assessment of home environment measured using standard HOME-SF scale at 18 months by a home visit	<p>HOME is a validated tool across cultures. The HOME-SF scale has 6 subscales: (1) parental responsiveness, (2) acceptance of the child, (3) organization of the environment, (4) learning materials, (5) parental involvement, and (6) variety in experience</p> <p>These align with the MAL-ED study which has also identified that a three-factor structure—emotional and verbal responsiveness, clean and safe environment, and child cleanliness—can be examined cross-culturally [49]</p>

Table 2 Outcome measurement schedule

Assessment schedule	Discharge	3mo	6mo	9mo	1 yr	15mo	18mo	21mo	2 yr to 3 yr
Motor impairment/cerebral palsy risk			X		X				X
Hearing impairment	X								
Vision impairment					X				
Mental, motor, social-emotional development									X
Epilepsy		X	X	X	X	X	X	X	X
Mortality		X	X	X	X	X	X	X	X
Weight			X		X				X
Infant length/child height			X		X				X
Head circumference			X		X				X
Feeding practices		X	X	X	X	X	X	X	X
Hospitalization admission at least overnight		X	X	X	X	X	X	X	X
Home environment							X		
Maternal depression			X		X				
Approximate duration of the study visit	30 min	30 min	45 min	20 min	60 min	20 min	30 min	20 min	60–90 min

process and the outcome measure assessments. Internal quality checks are conducted by the site coordinators and study principal investigators (PIs) at each site. The data acquisition for the outcome measurements is verified by the site coordinator. Ten percent of the data acquisition is reviewed by the expert investigator/designee for completeness and consistency. The investigators monitor at least 10% of processes being performed for different outcome measurements by the study conduct team. The observations are documented in specifically designed forms. Appropriate corrective and preventive actions are taken based on expert observations. External oversight and support is provided by WHO headquarters to ensure the quality of study implementation. This is done through site visits by WHO staff or consultants using a standardized monitoring checklist. Additionally, sites transfer data to WHO headquarters every month and this data is reviewed by the central team at WHO for quality, and feedback for improvement is provided to the PIs at respective sites.

Training and standardization

The research staff including the conduct team, project management team, data management, and internal quality control team underwent an intensive training before the start of the study. All were oriented to the protocol and GCP guidelines. Orientation and sensitization of regular health care staff of the Departments of Pediatrics, Physical Medicine and Rehabilitation, Ophthalmology and Ear, Nose and Throat regarding the study and its processes was done to ensure smooth functioning. The research staff has been provided role-specific intensive training and standardization. The research

assistants and coordinators from the conduct team were trained on screening for eligibility, administering written informed consent from the parents, enrolment, outcome measure assessments, and scheduling and tracking for the 3-year follow-up of the children to minimize deviations and non-compliance to the follow-up time points. All research staff were trained in rapport building and communication with the mother and the families. Training for specific outcome measurements like visual acuity using Teller Acuity Cards, hearing using screening ABR, and maternal depression using the 9-question patient health questionnaire (PHQ-9) was provided to the designated staff. There was a 2-week intensive training for Bayley's assessment by experts. A training of trainers (TOT) workshop for standardization of anthropometry measurements of length, head circumference, and weight was conducted by experts and the Safdarjung hospital, India investigators for all the five study sites. Each site was trained in the implementation of each tool, counseling of families if a neurodevelopmental impairment is identified with an appropriate referral system in place, and training local providers at each site.

All participating hospitals are supported to make quality-of-care improvement and provide standard of care with breast milk feeding support, complementary feeding support, and attention to hygiene for all infants.

Data collection

The data for the study is being collected on paper-based case report forms which are transcribed into an electronic database. The electronic database has been developed on a clinical data management platform "REDCap" with all the data quality checks. The questions, response

options, variable names, and data structure are identical for all sites. Double data entry is done at each site by trained entry personnel. The data manager at each site is responsible for data quality checks, query management, and ensuring completeness of data. Any discrepancies are addressed within 24 h of data collection. All data collected is password protected and stored in a local server in each site. No personal identifiers are entered in the database. All paper forms are stored in locked filing cabinets at the respective sites.

Data management and analysis

The data management is coordinated centrally by a team from WHO headquarters, but each site is responsible for site data management and data security. A central data repository has been created at the WHO headquarters. Sites share cleaned data every month to WHO where additional checks are run and a list of queries sent to the sites for clarification. All data sent to WHO does not have any personal identifiers.

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

General principles for analysis

The analysis will be by intention to treat. The primary outcome is a composite outcome comprising cerebral palsy, hearing impairment, vision impairment, cognitive, language, socio-emotional, adaptive and motor impairment, and epilepsy, and the presence of any one or more will be considered as neurodevelopmental impairment. However, during analyses, we will also consider each of these outcomes individually. Table 1 includes the scale/tool used for outcome measurement and wherever appropriate, the cutoffs of the scales, to indicate the presence or absence of the neurological impairment.

The primary and secondary outcomes will be compared between the intervention and control groups. All planned analysis will use a 5% significance level. Risk ratios and their confidence intervals will be calculated and will be the primary analysis if the loss to follow-up is 2.5% or lower. In case the loss to follow-up for the primary outcome is greater than 2.5%, we will additionally calculate hazard ratios and their confidence intervals. Additionally, we will adjust the results for confounding using multiple logistic regression and Cox proportional hazards models if there are any important differences in baseline characteristics between immediate KMC and control groups.

If more than 5% of data is missing from interim assessments, multiple imputation will be performed,

accounting for clustering by country with the number of imputations based on the percentage of missing data. Subgroup analysis will be conducted by (i) birth weight categories (1 to <1.2 kg, 1.2 to <1.5 kg, and 1.5 to <1.8 kg), (ii) gestation (<34, 34–36, ≥37 weeks), and (iii) singleton/multiple birth. Secondary analysis will be limited to an analysis by compliance. This secondary analysis will present the efficacy of the intervention by average duration of skin-to-skin contact over the first 3 days of life, categorized as ≥20 h/day, 10–19 h/day, and <10 h/day.

Study oversight

The study Steering Committee comprises all PIs from study sites, Bill and Melinda Gates Foundation representatives, and WHO technical staff functioning as its secretariat. This committee is responsible for designing and implementing the study in a harmonized way. Study PIs are responsible for contributing to the development of the research proposal, study manual, data management system, outcome measurement and data collection, data analysis and interpretation, and dissemination of results. All activities are facilitated and supported by WHO headquarters. On a fortnightly basis, the sites submit a brief status report to WHO. A formal progress report is submitted by each site every year.

The study is coordinated by a technical team from WHO headquarters, ensuring arrangements are in place to support teams in any challenges being faced to implement this study. WHO technical staff conducted intensive training at the beginning of the study. The technical team performs monitoring visits to each site every year. Monitoring visits have the dual function of identifying problems and supporting the sites in improving data collection, follow-up, and monitoring.

A Technical Advisory Group (TAG) has been set up in the field. The TAG members serve in their individual capacity and reviewed the final research protocol for any major concern prior to trial implementation. TAG members' terms of reference also include revision of manual of operations, study forms, and consent forms and advise on practical issues in implementing the trial in the field.

There is no data and safety monitoring board constituted for this study as this is a prospective follow-up study of a cohort of trial participants.

Discussion

This international multi-site study is the first of its kind aiming to assess the effect of immediate KMC on long-term outcomes. The literature has demonstrated an immediate benefit of KMC in stable neonates and is part of WHO guidelines for newborn care [5, 6]. More recently, the main iKMC trial showed that the benefits

of KMC can be extended to unstable low birth weight babies, beginning right at birth, and iKMC had a 25% lower risk of death at 28 days than those who received conventional care with Kangaroo Mother Care initiated after stabilization [12]. With the parent trial successfully conducted across these sites, there is no better opportunity to study the effect of this intervention on long-term outcomes. The follow-up study has the objective of elaborate and precise assessment of all the domains of neurodevelopment, including cerebral palsy (HINE), developmental delay (BSID III), hearing, vision, and epilepsy screening which would be evaluated by trained personnel ensuring optimal standardization on the large sample size in the five LMIC countries. The training and standardization conducted as part of this study have already strengthened the infrastructure and supported capacity building in the participating sites. This can be scaled up in the future at various tertiary centers in LMICs, in order to ensure quality, follow-up care for each and every mother-NICU/NICU graduate.

In addition, the final results will provide crucial insights and a higher level of evidence for the much-awaited long-term outcome of immediate KMC in the vulnerable sick low-birth-weight neonates. If proven effective, this intervention would be a value addition to the set of cost-effective strategies in reducing neurological impairment in resource-limited countries.

Study status

The trial is ongoing in all five sites—Ghana, India, Malawi, Nigeria, and Tanzania. The first participant was recruited on 11 January 2019. Participant recruitment and completion of all assessments are expected to be completed by 20 July 2022. The current protocol is version 3.2 dated 7 April 2021.

Abbreviations

KMC	Kangaroo Mother Care
iKMC	Immediate Kangaroo Mother Care
LMIC	Low- and middle-income countries
LBW	Low birth weight
WHO	World Health Organization
RCT	Randomized controlled trial
HINE	Hammersmith Infant Neurological Examination
BSID III	Bayley Scales of Infant and Toddler Development
ILAE	International League against Epilepsy
ABR	Auditory brainstem responses
IRB	Institutional Review Board
GCP	Good Clinical Practice
PI	Principal investigator
PHQ-9	Patient Health Questionnaire-9
TOT	Training of trainers
TAG	Technical Advisory Group

Acknowledgements

We acknowledge the contribution of Dr Augustine W Massawe, principal investigator from the Department of Paediatrics and Child Health, School of Medicine, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania. We are grateful to Dr Rajiv Bahl, Head of Research on Maternal, Newborn, Child and Adolescent Health and Newborn Unit Head, Department of Maternal, Newborn, Child and Adolescent Health and Ageing, World Health Organization, Geneva for his support and technical guidance. We thank the children and the families that have participated in the iKMC neurodevelopmental follow-up study. Our gratitude to all the staff members in all the participating sites. We also thank Mr Mukesh Juyal for secretarial support.

Trial registration

The iKMC neurodevelopment follow-up study is registered with the Clinical Trial Registry-India with number CTRI/2019/11/021899 on 06 November 2019.

Authors' contributions

All named authors contributed to protocol development, drafting the manuscript, and review of the manuscript for intellectual content; approved the final version of the manuscript; and have agreed to publication. All authors agree to adhere to the authorship guidelines of *Trials*.

TD is a staff member of the World Health Organization (WHO). The author alone is responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the WHO.

Funding

The study has been granted funding from the Bill and Melinda Gates Foundation. The funders had no role in the study design, protocol development, or study implementation and will have no role in analyses, interpretation of data, or decision to submit the results.

Availability of data and materials

The datasets generated during the current study will be available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Since this is a multi-country, multicenter study with a single protocol, approvals on the same protocol have been obtained from the WHO Ethics Review Committee (reference no. EC0002910 approved on 23 Nov 2017) as well as the local Institutional Review Boards (IRBs) of the five participating hospital sites: Ghana's School of Medical Sciences/Komfo Anokye Teaching Hospital Committee on Human Research, Publication and Ethics (reference number CHRPE/AP/170/19, initial approval on 11 April 2019), Tanzania's National Institute for Medical Research (reference number NIMR/HQ/R.8c/Vol. I/708, initial approval on 17 June 2019), Malawi's College of Medicine Research and Ethics Committee (COMREC) (reference number P.08/17/2235, initial approval on 21 April 2020), Nigeria's OAUTHC Ethics and Research Committee (reference number IRB/IEC/0004553, approval on 30 May 2019), and New Delhi-India's Vardhman Mahavir Medical College and Safdarjung Hospital Institutional Ethics Committee (reference number IEC/VMMC/SJH/Project/2019-06/52, initial approval on 21 October 2019). Each updated version of the protocol was approved by each of the above-mentioned ethics committees.

A verbal consent was taken from the parents during the 29-day follow-up visit in the main iKMC trial, and a written informed consent for participation in the follow-up study is obtained at the time of initiation of the 3-year follow-up.

Consent for publication

Not relevant.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife 220005, Nigeria. ²Komfo Anokye Teaching Hospital, P.O. Box 1934, Adum, Kumasi, Ghana. ³Department of Pediatrics, Vardhman Mahavir Medical College and Safdarjung Hospital, Ansari Nagar, New Delhi 110029, India. ⁴Department of Paediatrics and Child Health, School of Medicine, Muhimbili University

of Health and Allied Sciences, Dar Es Salaam 255, Tanzania. ⁵Vardhman Mahavir Medical College and Safdarjung Hospital, Ansari Nagar, New Delhi 110029, India. ⁶Department of Child Health, Komfo Anokye Teaching Hospital, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana. ⁷Queen Elizabeth Central Hospital, Blantyre, Malawi. ⁸Department of Mental Health and Substance Use, World Health Organization, Geneva, Switzerland. ⁹Department of Obstetrics and Gynaecology, Kamuzu University of Health Sciences, Blantyre, Malawi. ¹⁰Department of Paediatrics and Child Health, Kamuzu University of Health Sciences, Blantyre, Malawi. ¹¹Atal Bihari Vajpayee Institute of Medical Sciences & Dr Ram Manohar Lohia Hospital, New Delhi 110001, India. ¹²School of Public Health, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana. ¹³Research and Development, Komfo Anokye Teaching Hospital, P.O. Box 1934, Adum, Kumasi, Ghana. ¹⁴Department of Psychiatry, Child And Adolescent Mental Health, Komfo Anokye Teaching Hospital, P.O. Box 1934, Adum, Kumasi, Ghana. ¹⁵Division of Epilepsy & Clinical Neurophysiology, Boston Children's Hospital, Harvard Medical School, Boston, USA. ¹⁶Clinical Development Services Agency (CDSA), Translational Health Science and Technology Institute (THSTI), NCR Biotech Science Cluster, PO Box #04, Faridabad 121001, India. ¹⁷Translational Health Science and Technology Institute (THSTI), NCR Biotech Science Cluster, PO Box #04, 121001 Faridabad, India. ¹⁸Faridabad-Gurgaon Expressway, Translational Health Science and Technology Institute, NCR Biotech Science Cluster, 3Rd Milestone Post Box #04, Faridabad, Haryana 121001, India.

Received: 28 July 2022 Accepted: 20 February 2023

Published online: 10 April 2023

References

- World Health Organization & United Nations Children's Fund (UNICEF). Low birthweight : country, regional and global estimates [Internet]. 2004. World Health Organization [cited 29 Jun 2022]. Available from: <https://apps.who.int/iris/handle/10665/43184>.
- Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? *Lancet*. 2005;365(9462):891–900.
- Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol*. 2007;196(2):147.e1-8.
- Younge N, Goldstein RF, Bann CM, Hintz SR, Patel RM, Smith PB, et al. Survival and neurodevelopmental outcomes among periviable infants. *N Engl J Med*. 2017;376(7):617–28.
- Kangaroo mother care: a practical guide [Internet]. [cited 29 Jun 2022]. Available from: <https://www.who.int/publications-detail-redirect/9241590351>
- WHO recommendations on interventions to improve preterm birth outcomes [Internet]. Geneva: World Health Organization; 2015 [cited 29 Jun 2022]. (WHO Guidelines Approved by the Guidelines Review Committee). Available from: <http://www.ncbi.nlm.nih.gov/books/NBK321160/>
- Conde-Agudelo A, Diaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev*. 2016; 2016(8):CD002771.
- Worku B, Kassie A. Kangaroo mother care: a randomized controlled trial on effectiveness of early kangaroo mother care for the low birthweight infants in Addis Ababa. *Ethiopia J Trop Pediatr*. 2005;51(2):93–7.
- Bergman NJ, Linley LL, Fawcus SR. Randomized controlled trial of skin-to-skin contact from birth versus conventional incubator for physiological stabilization in 1200- to 2199-gram newborns. *Acta Paediatr*. 2004;93(6):779–85.
- Chi Luong K, Long Nguyen T, Huynh Thi DH, Carrara HPO, Bergman NJ. Newly born low birthweight infants stabilise better in skin-to-skin contact than when separated from their mothers: a randomised controlled trial. *Acta Paediatr*. 2016;105(4):381–90.
- WHO Immediate KMC Study Group. 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. *Trials*. 2020 ;21(1):280.
- WHO Immediate KMC Study Group, Arya S, Naburi H, Kawaza K, Newton S, Anyabolu CH, et al. Immediate 'Kangaroo Mother Care' and survival of infants with low birth weight. *N Engl J Med*. 2021;384(21):2028–38.
- Mitchell AJ, Yates C, Williams K, Hall RW. Effects of daily kangaroo care on cardiorespiratory parameters in preterm infants. *J Neonatal Perinatal Med*. 2013;6(3):243–9.
- Silva MG de C, Barros MC de M, Pessoa ÚML, Guinsburg R. Kangaroo-mother care method and neurobehavior of preterm infants. *Early Hum Dev*. 2016;95:55–9.
- Doddabasappa PN, Mahantshetti NS, Kamate M, E A. Effect of kangaroo mother care on neurodevelopmental outcome of low birth weight babies: a one-year randomized control trial. *Int J Contemp Pediatr*. 2018 ;5(2):508–14.
- Wang Y, Zhao T, Zhang Y, Li S, Cong X. Positive effects of Kangaroo Mother Care on long-term breastfeeding rates, growth, and neurodevelopment in preterm infants. *Breastfeed Med*. 2021;16(4):282–91.
- Chapak N, Tessier R, Ruiz JG, Hernandez JT, Uriza F, Villegas J, et al. Twenty-year follow-up of kangaroo mother care versus traditional care. *Pediatrics*. 2017;139(1): e20162063.
- Baley J, COMMITTEE ON FETUS AND NEWBORN. Skin-to-skin care for term and preterm infants in the neonatal ICU. *Pediatrics*. 2015 ;136(3):596–9.
- Head LM. The effect of kangaroo care on neurodevelopmental outcomes in preterm infants. *J Perinat Neonatal Nurs*. 2014 ;28(4):290–9; quiz E3–4.
- Lester BM, Salisbury AL, Hawes K, Dansereau LM, Bigsby R, Laptook A, et al. 18-Month follow-up of infants cared for in a single-family room neonatal intensive care unit. *J Pediatr*. 2016;177:84–9.
- Ohgi S, Fukuda M, Moriuchi H, Kusumoto T, Akiyama T, Nugent JK, et al. Comparison of kangaroo care and standard care: behavioral organization, development, and temperament in healthy, low-birth-weight infants through 1 year. *J Perinatol*. 2002;22(5):374–9.
- Kaffashi F, Scher MS, Ludington-Hoe SM, Loparo KA. An analysis of the kangaroo care intervention using neonatal EEG complexity: a preliminary study. *Clin Neurophysiol*. 2013;124(2):238–46.
- Scher MS, Ludington-Hoe S, Kaffashi F, Johnson MW, Holditch-Davis D, Loparo KA. Neurophysiologic assessment of brain maturation after an 8-week trial of skin-to-skin contact on preterm infants. *Clin Neurophysiol*. 2009;120(10):1812–8.
- Feldman R, Rosenthal Z, Eidelman AI. Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. *Biol Psychiatry*. 2014;75(1):56–64.
- Sukumaran TU, Vijesh PV, Sukumaran PS. Developmental delay and disabilities in high risk new borns-a follow up study. *J Rehab Council India*. 2008;4(1–2):18–24.
- Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. *Pediatrics*. 2000;105(6):1216–26.
- Arora NK, Nair MKC, Gulati S, Deshmukh V, Mohapatra A, Mishra D, et al. Neurodevelopmental disorders in children aged 2–9 years: population-based burden estimates across five regions in India. *PLoS Med*. 2018;15(7): e1002615.
- Bayley Scales of Infant and Toddler Development | Third Edition [Internet]. [cited 29 Jun 2022]. Available from: <https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Behavior/Adaptive/Bayley-Scales-of-Infant-and-Toddler-Development-%7C-Third-Edition/p/100000123.html>
- Hutchings J, Potterton J. Developmental delay in HIV-exposed infants in Harare. *Zimbabwe Vulnerable Children Youth Stud*. 2014;9(1):43–55.
- Ballot DE, Ramdin T, Rakotsoane D, Agaba F, Davies VA, Chirwa T, et al. Use of the Bayley Scales of Infant and Toddler Development, third edition, to assess developmental outcome in infants and young children in an urban setting in South Africa. *Int Sch Res Notices*. 2017;2017:1631760.
- Johnson S, Moore T, Marlow N. Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used? *Pediatr Res*. 2014;75(5):670–4.
- Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. *JAMA Pediatr*. 2017;171(9):897–907.
- Romeo DMM, Cioni M, Scoto M, Mazzone L, Palermo F, Romeo MG. Neuromotor development in infants with cerebral palsy investigated by the Hammersmith Infant Neurological Examination during the first year of age. *Eur J Paediatr Neurol*. 2008;12(1):24–31.

34. Pizzardi A, Romeo DMM, Cioni M, Romeo MG, Guzzetta A. Infant neurological examination from 3 to 12 months: predictive value of the single items. *Neuropediatrics*. 2008;39(6):344–6.
35. Romeo DM, Ricci D, Brogna C, Mercuri E. Use of the Hammersmith Infant Neurological Examination in infants with cerebral palsy: a critical review of the literature. *Dev Med Child Neurol*. 2016;58(3):240–5.
36. Romeo DMM, Cioni M, Palermo F, Cilauro S, Romeo MG. Neurological assessment in infants discharged from a neonatal intensive care unit. *Eur J Paediatr Neurol*. 2013;17(2):192–8.
37. Haataja L, Mercuri E, Regev R, Cowan F, Rutherford M, Dubowitz V, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. *J Pediatr*. 1999;135(2 Pt 1):153–61.
38. Maitre NL, Chorna O, Romeo DM, Guzzetta A. Implementation of the Hammersmith Infant Neurological Examination in a High-Risk Infant Follow-Up Program. *Pediatr Neurol*. 2016;65:31–8.
39. From National Consultation Meeting for Developing IAP Guidelines on Neurodevelopmental Disorders under the aegis of IAP Childhood Disability Group and the Committee on Child Development and Neurodevelopmental Disorders, Paul A, Prasad C, Kamath SS, Dalwai S, C Nair MK, et al. Consensus Statement of the Indian Academy of Pediatrics on Newborn Hearing Screening. *Indian Pediatr*. 2017 ;54(8):647–51.
40. Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics*. 2007;120(4):898–921.
41. Harlor ADB, Bower C, Committee on Practice and Ambulatory Medicine, Section on Otolaryngology-Head and Neck Surgery. Hearing assessment in infants and children: recommendations beyond neonatal screening. *Pediatrics*. 2009 ;124(4):1252–63.
42. Newborn and infant hearing screening: current issues and guiding principles for action [Internet]. [cited 29 Jun 2022]. Available from: <https://www.who.int/publications-detail-redirect/9789241599496>
43. Stout AU, Wright KW. Pediatric eye examination. In: Wright KW, editor. *Pediatric Ophthalmology and strabismus*. St. Louis, MO: C.V. Mosby; 1995. p. 63–72.
44. Committee on practice and ambulatory medicine, section on ophthalmology, American Association of Certified Orthoptists, American Association for Pediatric Ophthalmology and strabismus, American Academy of Ophthalmology, Simon GR, et al. Visual system assessment in infants, children, and young adults by pediatricians. *Pediatrics*. 2016;137(1):e20153596.
45. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475–82.
46. Ottman R, Barker-Cummings C, Leibson CL, Vasoli VM, Hauser WA, Buchhalter JR. Validation of a brief screening instrument for the ascertainment of epilepsy. *Epilepsia*. 2010;51(2):191–7.
47. Diagnosis of convulsive epilepsy by non-specialist health care providers. [Internet]. [cited 4 Jul 2022]. Available from: <https://www.medbox.org/document/diagnosis-of-convulsive-epilepsy-by-non-specialist-health-care-providers#GO>
48. Yawn BP, Bertram S, Kurland M, Wollan PC. Repeated depression screening during the first postpartum year. *Ann Fam Med*. 2015;13(3):228–34.
49. Jones PC, Pendergast LL, Schaefer BA, Rasheed M, Svensen E, Scharf R, et al. Measuring home environments across cultures: invariance of the HOME scale across eight international sites from the MAL-ED study. *J Sch Psychol*. 2017;64:109–27.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

