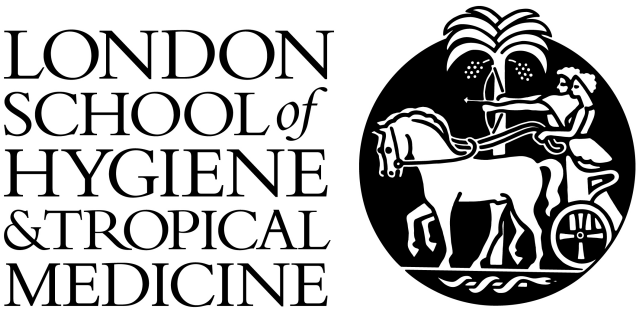

Informing the design of a trial of kangaroo mother care initiated before stabilisation amongst small and sick newborns in a sub-Saharan African context using mixed methods

Dr Melissa Morgan Medvedev

Thesis submitted in accordance with the requirements for the degree of Doctor of Philosophy of the University of London

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Declaration of own work

I, Melissa Morgan Medvedev, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: [redacted] ____ Date: 13 August 2020

Table A1-1 provides a detailed overview of my role in each part of this thesis.

Abstract

An estimated 2.5 million neonates die every year, with preterm birth being the leading cause. Sub-Saharan Africa and southern Asia account for 78% of neonatal deaths. The WHO recommends kangaroo mother care (KMC) for stabilised newborns ≤2000g; however, most deaths occur *before stabilisation*. An evidence gap exists regarding KMC for this population.

The overall aim of this PhD was to inform the design of a trial of KMC initiated before stabilisation in a sub-Saharan African context. The first part focused on assessing facility readiness and quantifying neonatal mortality risk. Cascade models were developed and used to assess 23 East African facilities. A logistic model was derived and validated using data from 187 UK hospitals and one Gambian hospital. The final model, including three parameters, demonstrated very good performance. The score requires further validation in low-resource contexts, but has potential to improve neonatal resource allocation.

The second part of this PhD focused on evaluating the feasibility of initiating KMC before stabilisation and designing the trial. This study showed it was feasible to monitor and provide care in the KMC position, and found the intervention was acceptable to parents and providers. Launched in 2020, the OMWaNA trial will determine the mortality impact of this intervention within 7 days relative to standard care at four Ugandan hospitals. Process and economic evaluations will explore causal pathways for clinical effects, estimate incremental cost and cost-effectiveness, and examine barriers and facilitators to inform uptake and sustainability.

This PhD has developed a cascade model to assess facility readiness, validated a score to assess individual risk, and demonstrated the feasibility of initiating KMC before stabilisation. These studies have informed the design of a trial evaluating the mortality impact of this intervention in Uganda. The findings are expected to have broad applicability to low-resource hospitals and important policy implications.

Acknowledgements

This PhD has been an amazing journey, and I have been fortunate to work with many wonderful people along the way. This work would not have been possible without my two extraordinary supervisors; Elizabeth Allen, who has provided invaluable support and guidance on statistical modelling and trial design throughout the course of this PhD; and Joy Lawn, my mentor for the past five years, whose passion, expertise, and vision for improving newborn health worldwide launched the evidence base upon which the trial and other studies in this PhD were developed.

I am thankful to Diana Elbourne for being part of my advisory committee, sharing her wisdom on neonatal trials (as well as her office during the first 6 months of this PhD), and providing timely feedback on every document I have asked her to read. I am indebted to Peter Waiswa, a member of my advisory committee and an advocate for newborn health in Uganda, for his unwavering support of my research and his valuable insights. I am grateful to Cally Tann, another member of my advisory committee, for her instrumental advice and support at different stages of this PhD.

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Finally, my deepest thanks go to my partner Dmitry for his unwavering support, and to my parents for always encouraging me to follow my dreams.

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List of Figures

Footnote: With the exception of Figure 6-1 and Figures 7-1 to 7-3, figures from Chapters 3, 4, 6, and 7 are embedded in the PDF of the published paper and are excluded from the list above. A list of these figures can be found on the first page of the relevant chapter.

Abbreviations

AE	Adverse event
ARR	Annualised rate of reduction
bpm	Beats per minute
C	Celsius
CI	Confidence interval
CPAP	Continuous positive airway pressure
CRIB	Clinical Risk Index for Babies
d	Day
DSMB	Data and Safety Monitoring Board
EEG	Electroencephalogram
EFSTH	Edward Francis Small Teaching Hospital
eKMC	Early Kangaroo Mother Care
ELBW	Extremely low birthweight
EmONC	Emergency Obstetric and Newborn Care
ENAP	Every Newborn Action Plan
EOC	Essential Obstetric Care
FIC	Family-integrated care
g	Grams
GCP	Good Clinical Practice
h	Hours
HC	Head circumference
HPA	Hypothalamic-pituitary-adrenal
HR	Heart rate
iKMC	Immediate Kangaroo Mother Care trial
IPISTOSS	Immediate Parent Infant Skin-to-Skin Study
IRB	Institutional Review Board
IQR	Interquartile range
IV	Intravenous
IVH	Intraventricular haemorrhage
JRRH	Jinja Regional Referral Hospital
L	Litre
LBW	Low birthweight
LMIC	Low- and middle-income country
LMP	Last menstrual period
LOS	Length of stay
LSHTM	London School of Hygiene & Tropical Medicine
KMC	Kangaroo mother care
kg	Kilogram
MDG	Millennium Development Goal
MIRI	Maternal Infant Responsiveness Instrument
mL	Millilitre
mmol	Millimole
MRC	Medical Research Council
NA	Not applicable
NEST	Newborn Essential Solutions and Technologies
NMR-2000	Neonatal Mortality Risk amongst newborns ≤2000g
NICU	Neonatal intensive care unit
NNRD	National Neonatal Research Database
NPV	Negative predictive value

NSCU	Newborn special care unit
NTISS	Neonatal Therapeutic Intervention Scoring System
OMWaNA	Operationalising kangaroo Mother care before stabilisation amongst low birth Weight neonates in Africa trial
OR	Odds ratio
PI	Principal Investigator
PIPP	Premature Infant Pain Profile
PMTCT	Prevention of mother-to-child transmission
PNFP	Private not-for-profit
PPV	Positive predictive value
RCT	Randomised controlled trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
ROC	Receiver operating characteristic
ROP	Retinopathy of prematurity
RR	Relative risk
SAE	Serious adverse event
SAWS	Simplified age-weight-sex
SCRIP	Stability of the Cardio-Respiratory system In Premature infants
SD	Standard deviation
SDG	Sustainable Development Goal
SGA	Small-for-gestational age
SNAP	Score for Neonatal Acute Physiology
SNAPPE	Score for Neonatal Acute Physiology-Perinatal Extension
SOP	Standard operating procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SpO_2	Oxygen saturation measured by pulse oximetry
SSC	Skin-to-skin contact
TIDieR	Template for intervention description and replication
TRIPS	Transport Risk Index of Physiologic Stability
TSC	Trial Steering Committee
UCSF	University of California San Francisco
UK	United Kingdom
UN	United Nations
UNCST	Uganda National Council of Science and Technology
UNICEF	United Nations Children's Fund
US	United States
UVRI	Uganda Virus Research Institute
VLBW	Very low birthweight
WCI	Women's Capabilities Index
WHO	World Health Organisation

Definitions

Adverse event: any untoward medical occurrence in a patient or clinical investigation subject administered an experimental therapy, which does not necessarily have to have a causal relationship with this therapy[1]

Apgar score: system for assessing newborns and response to neonatal resuscitation at the time of delivery; includes 5 components: 1) colour, 2) heart rate, 3) reflexes, 4) muscle tone, 5) respiration; each component is scored 0 to 2 at 1 and 5 minutes post-birth, and at 5-minute intervals thereafter up to 20 minutes for infants scoring <7[2]

Apnoea of prematurity: a pause of breathing lasting >15–20 seconds, or accompanied by oxygen desaturation (SpO_2 ≤80% for ≥4 seconds) and bradycardia (HR <2/3 of baseline for ≥4 seconds), in a preterm infant[3]

Breastmilk feeding: process of feeding a mother's breastmilk to her infant, either directly from the breast or by expressing milk from the breast and feeding it to the infant by nasogastric tube, bottle, cup, or spoon, to provide calories, macronutrients, and micronutrients[4]

Hypoglycaemia: blood glucose concentration <2.6 mmol/L; increased risk in newborns who are preterm, small-for-gestational age, or sick, and those born to diabetic mothers; highest risk within first 24 hours after birth, as newborns transition to extrauterine life; failure to achieve or maintain normoglycaemia may be related to inadequate glycogen stores, immature glycogenolytic or gluconeogenic pathways, and/or poor endocrine adaptation (e.g., transient hyperinsulinism)[5]

Hypothermia: body temperature below the normal range (36.5°C – 37.5°C); low birthweight and sick newborns are at higher risk because they regulate body temperature less well than normal birthweight babies; can be sub-categorised as follows:[6]

Mild hypothermia: 36.0°C – 36.4°C

Moderate hypothermia: 32.0°C – 35.9°C

Severe hypothermia: <32.0°C

Intraventricular haemorrhage: complication of prematurity characterised by bleeding within the ventricles (fluid-filled areas) inside the brain, typically originating from the periventricular germinal matrix (a highly vascular collection of neuronal-glial precursor cells); majority of

affected infants are asymptomatic; diagnosis is based on screening cranial ultrasound; severity ranges from grade 1 (mild) to grade 4 (severe)[7]

Kangaroo mother care: Package of care that consists of prolonged skin-to-skin contact (SSC) between neonate and caregiver, usually the mother; promotion of exclusive breast milk feeding; early hospital discharge; and adequate support and close follow-up at home[8]

Continuous KMC: SSC between baby and caregiver for at least 18h/day

Intermittent KMC: SSC between baby and caregiver for periodic sessions of ≥1h duration

Length of stay: duration of hospitalisation

Low birthweight: live newborn with birthweight <2500g; can be sub-categorised as follows:[9]

Very low birthweight: birthweight <1500g

Extremely low birthweight: birthweight <1000g

Neonatal mortality rate: number of neonates dying before reaching 28 days of age, per 1,000 live births in a year[10]

Neonatal period: first 28 days post-birth; can be sub-categorised as follows:[11]

Early neonatal period: 0-6 days post-birth

Late neonatal period: 7-28 days post-birth

Preterm: live birth before 37 completed weeks gestation; can be sub-categorised as follows:[12]

Extremely preterm: birth at <28 weeks

Very preterm: birth at 28 to <32 weeks

Moderate to late preterm: 32 to <37 weeks

Serious adverse event: any untoward medical occurrence that 1) results in death, 2) is life threatening, 3) requires prolongation of hospitalisation, 4) results in persistent or significant disability/incapacity, or 5) is a congenital anomaly/birth defect[1]

Thermal protection of the newborn: series of measures taken at birth and during first few days post-birth to ensure newborns maintain normal body temperature of 36.5-37.5°C[6]

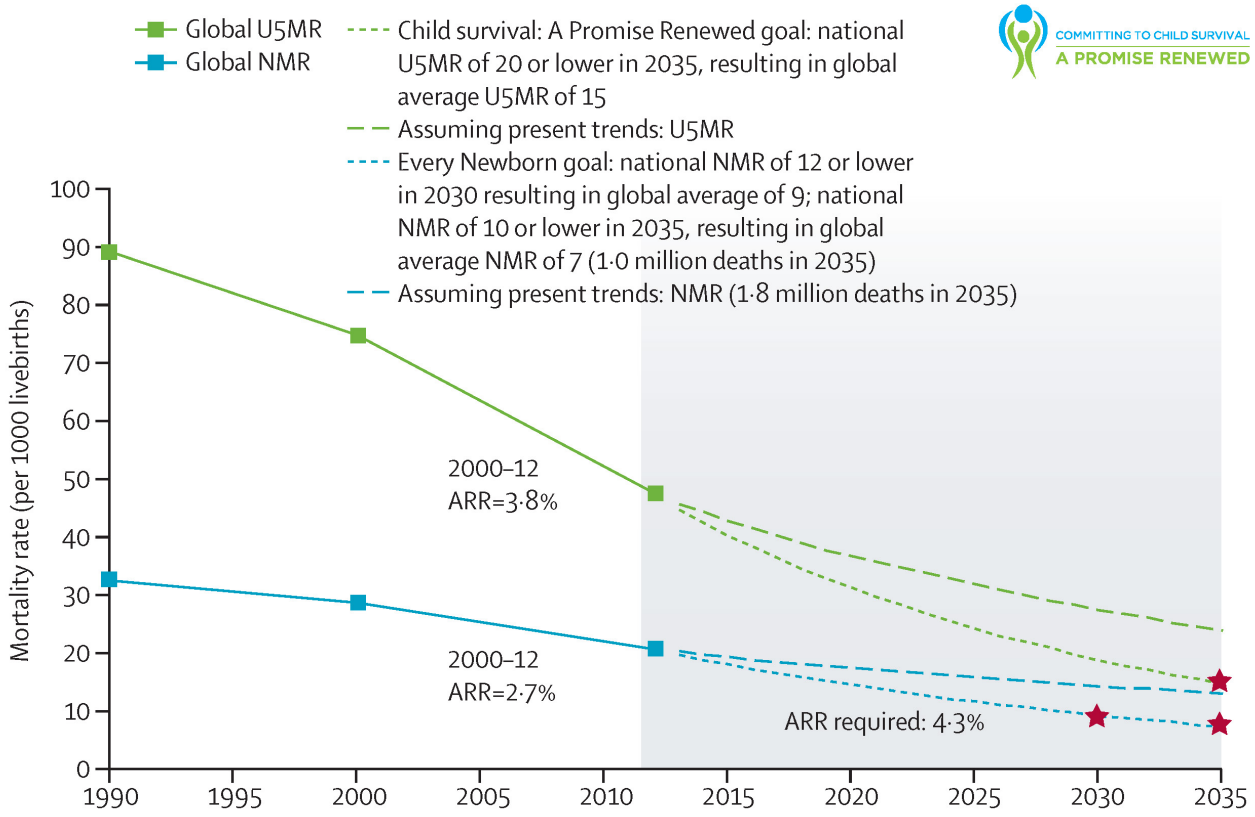
1. Background and rationale

1.1. Global neonatal mortality

Between 1990 and 2015, the mortality rate amongst children under 5 years of age declined by 53% globally. Despite this accomplishment, the global community failed to achieve the two-thirds reduction targeted by Millennium Development Goal (MDG) 4.[13] Slower progress in reducing neonatal deaths (deaths within 28 days of birth) largely explains why this target was not reached. Despite a 3-fold increase in donor assistance for maternal, newborn, and child health projects and a 34-fold increase for programmes including newborns in the target population,[14] the annualised rate of reduction (ARR) for all-cause neonatal mortality between 2000 and 2015 (3.1%) was much lower than that for children aged 1–59 months (4.7%).[15] Consequently, the proportion of neonatal deaths increased from 39% to 45% over the same period.[15]

Post-2015, the global health community witnessed a shift from the MDGs to the Sustainable Development Goals (SDG), including a central focus on closing the equity gap ("leave no one behind").[16] In line with this priority, the SDGs include a target neonatal mortality rate of ≤12 per 1000 livebirths and an under-5 mortality rate of ≤25 per 1000 livebirths in all countries by 2030.[17] Growing recognition of the global burden of neonatal death and disability, including adverse effects on human capital and wellbeing, led to the development of the United Nations (UN) Secretary General's Every Newborn Action Plan (ENAP).[18] Endorsed at the World Health Assembly in 2014, the ENAP is a country-led, multi-partner initiative that aims to end preventable newborn deaths and stillbirths, with national targets of ≤10 neonatal deaths per 1000 livebirths and ≤10 stillbirths per 1000 total births by 2035.[19] The ENAP neonatal mortality target was selected in consideration of the corresponding under-5 target of ≤25 deaths per 1000 livebirths in the SDGs. Based on trends between 2000 and 2012, a global ARR of 4.3% will be required to achieve the SDG and ENAP neonatal mortality targets by 2030 (Figure 1-1).[18]

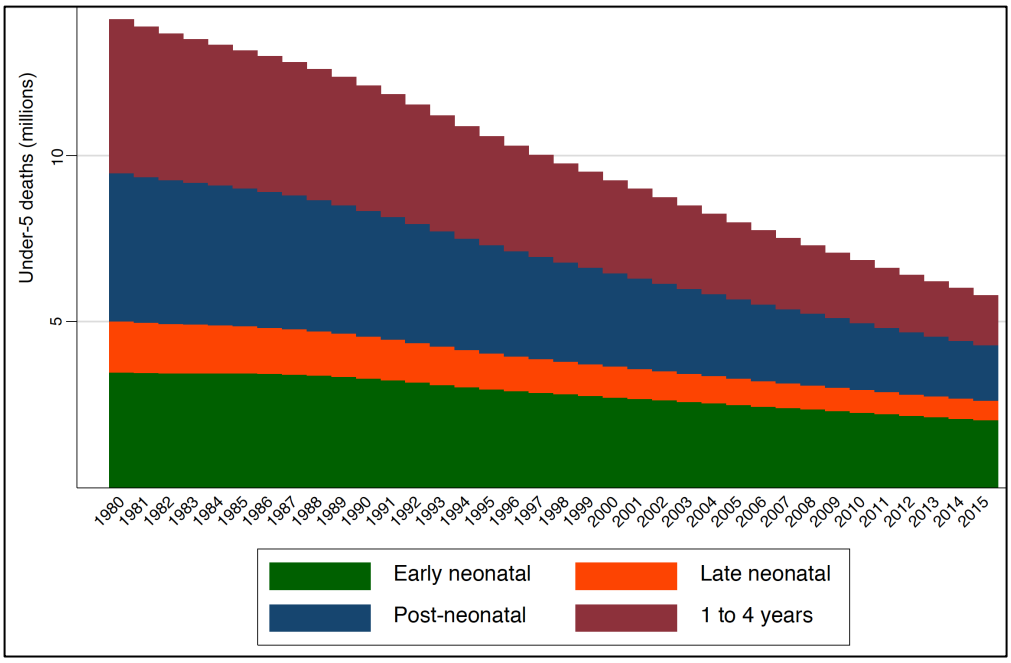
Figure 1-1. Mortality trends from 1990 to 2012, and neonatal mortality targets by 2030 set by the Every Newborn Action Plan



Source: Lawn et al, 2014.[18] Estimates for under-5 mortality rate (U5MR) and neonatal mortality rate (NMR) to 2012 based on data from the UN Interagency Group for Child Mortality Estimation (UN-IGME). Projections to 2035 based on ARRs for 2000-2012, with global numbers representing aggregation of country-specific numbers and projections.

An estimated 2.5 million neonatal deaths occurred in 2018, accounting for 47% of under-5 deaths.[20] The neonatal mortality rate was estimated at 18 per 1000 livebirths globally (2018).[20] The neonatal period represents the time of highest mortality risk amongst children and adolescents aged <15 years. Within the neonatal period, 36% of deaths occur within 24 hours (h) of birth and 73% occur in the early neonatal period, defined as the first 7 days of life.[11] Between 1980 and 2015, early neonatal mortality decreased more slowly than all other categories of under-5 deaths (Figure 1-2).[21] Complications of preterm birth, defined as birth before 37 completed weeks of gestation, are the leading cause, accounting for 35% of neonatal deaths and 16% of under-5 deaths (Figure 1-3).[20]

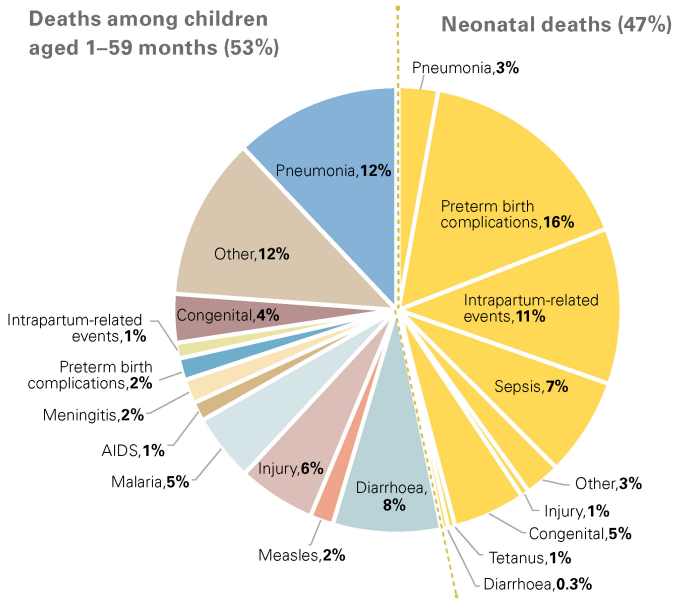
Figure 1-2. Global age pattern of under-5 mortality, 1980-2015



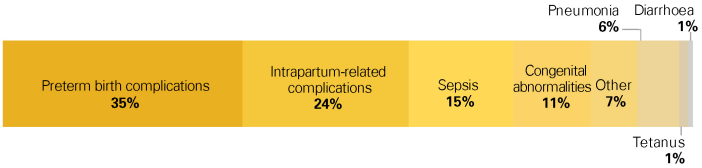
Source: Global Burden of Disease Child Mortality Collaborators, 2015.[21]

Figure 1-3. Global distribution of under-5 and neonatal deaths by cause, 2018

A. Global distribution of deaths among children under age 5, by cause, 2018



B. Global distribution of newborn deaths by cause, 2018



Source: UN Interagency Group for Child Mortality Estimation, 2019.[20] Estimates from WHO and the Maternal and Child Epidemiology Estimation Group, based on cause fractions for 2017 applied to UN-IGME estimates for 2018.

1.2. Mortality in preterm and low birthweight neonates

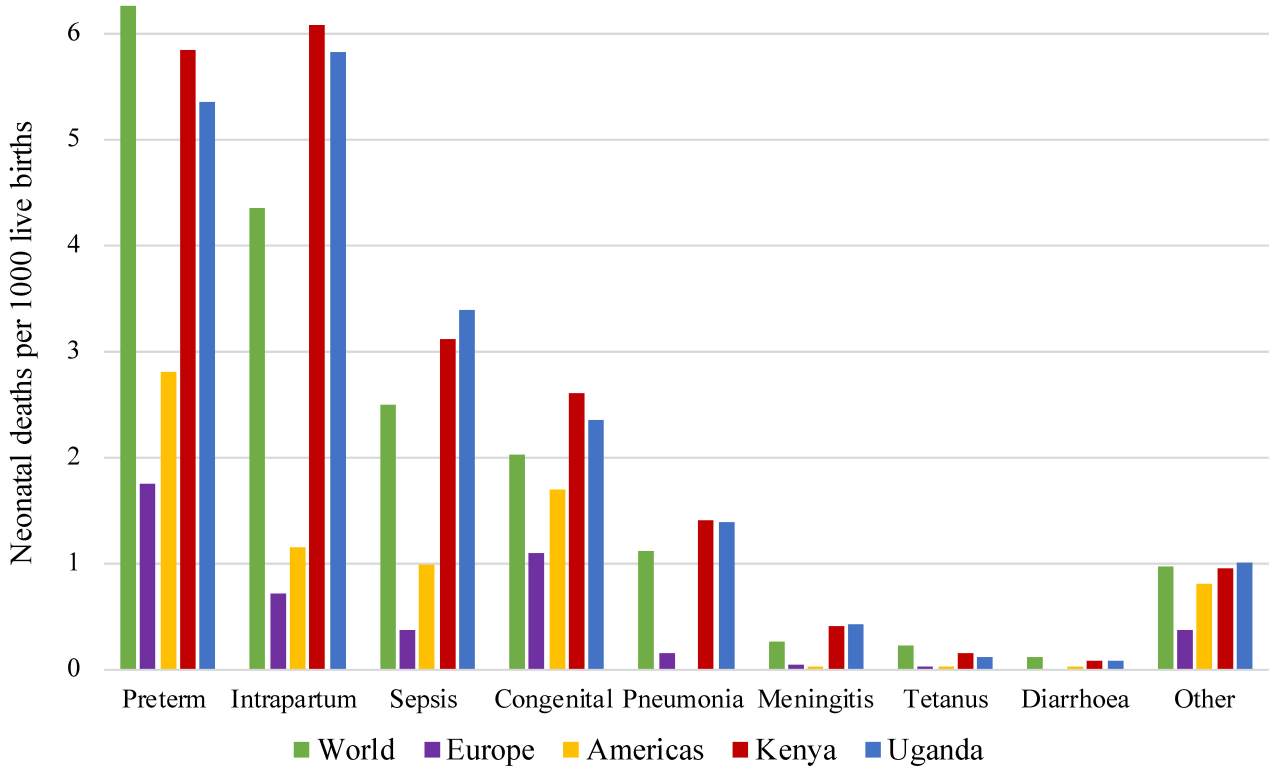
Globally, 14.8 million babies are born preterm and 20.5 million are born with low birthweight [LBW, <2500 grams (g)] every year.[22,23] Over 80% of neonatal deaths occur in LBW babies, among which two-thirds are preterm and one-third are term and small-for-gestational age (SGA).[23–25] Neonatal mortality is 15-fold higher in SGA preterm babies relative to babies with either characteristic alone.[24] Major mortality reduction could be achieved by improving inpatient care in LMICs.[18,26–28] In such settings, 50% of neonates born at 32-34 weeks' gestation, a time when nearly all should survive, die because adequate care is not available.[26,29]

1.3. Neonatal mortality in sub-Saharan Africa, Kenya, and Uganda

Nearly 80% of neonatal deaths occur in sub-Saharan Africa and southern Asia.[20] Compared to other regions, sub-Saharan Africa has experienced slow progress in reducing newborn deaths, particularly those due to complications of prematurity.[15,30] The ARR for all-cause neonatal mortality in sub-Saharan Africa between 2000 and 2018 (2.1%) was nearly 50% lower than that for children aged 1–59 months (3.8%).[20] This disparity is likely related to higher rates of preterm birth and LBW,[18,22,23] poor coverage of facility-based neonatal care,[26,29,31,32] and health system capacity issues, including physical and human resource deficiencies.[33–36] Further, many interventions are introduced without adequate evidence of their effectiveness in related LMIC contexts.[26,37]

In Kenya and Uganda, neonatal mortality rates were estimated at 19.6 and 19.9 per 1000 livebirths, respectively, with a resultant 28,911 and 32,296 deaths in 2018.[20] Complications of prematurity were a leading cause of neonatal deaths in Kenya and Uganda with estimated cause-specific mortality rates of 5.8 and 5.4 per 1000 live births, respectively, approximately two-fold higher than that of the Americas and three-fold higher than that of Europe (Figure 1-4).[38] Paralleling the global trend, 37% of neonatal deaths in sub-Saharan Africa occur on the day of birth and 74% occur in the first week.[11]

Figure 1-4. Causes of neonatal death (2017): Worldwide, Europe, the Americas, Kenya, and Uganda



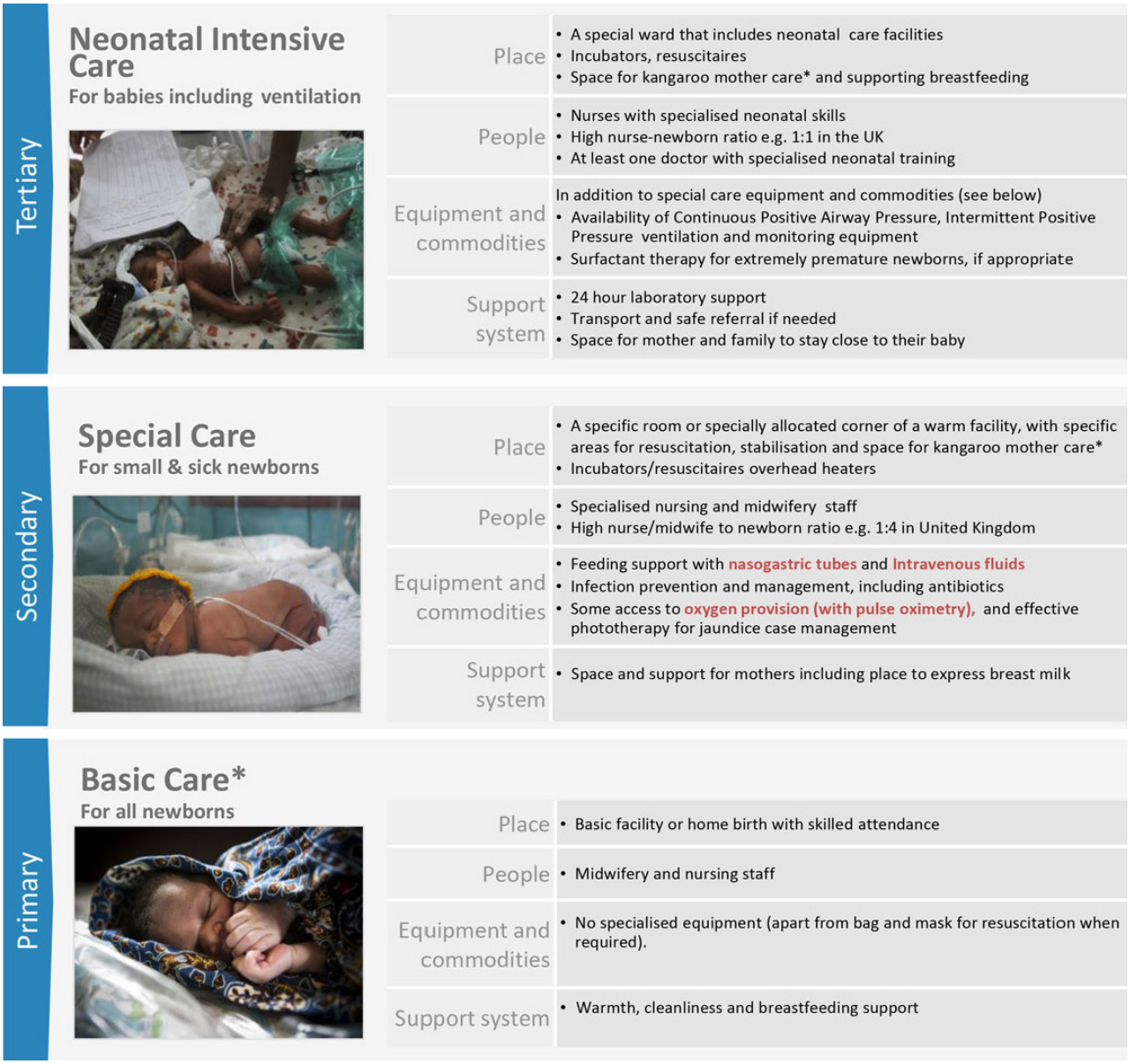
Source of data: WHO and the Maternal and Child Epidemiology Estimation Group, 2018.[38]

1.4. Levels of neonatal inpatient care

In an effective health system, neonatal care is typically delivered across three levels (Figure 1-5).[34] Essential newborn care, which should be provided to all babies, includes bag-mask resuscitation (for babies who do not breathe at birth), thermal support (drying, warming), hygienic cord and skin care, and early initiation of exclusive breastfeeding.[26] Special care refers to a package of facility-based interventions for small and sick newborns, which includes bag-mask resuscitation and overhead heaters (for neonates requiring stabilisation); thermal support with kangaroo mother care (KMC); feeding support with intravenous (IV) fluids and nasogastric tubes; infection prevention and treatment with antibiotics; oxygen therapy and pulse oximetry monitoring for respiratory distress; and phototherapy for jaundice.[26,34] Estimates suggest that achieving 95% coverage of these interventions in 81 high-burden countries could prevent 747,400 neonatal deaths in 2030, and reduce prematurity-, intrapartum-, and infection-related causes of mortality by 86%, 76%, and 74%, respectively (Figure 1-6).[39] Located in tertiary hospitals, neonatal intensive care units (NICU) are staffed by providers with specialised neonatal skills and additionally offer continuous positive airway pressure (CPAP) or mechanical ventilation, surfactant therapy (for preterm babies with severe respiratory distress),[26,40] 24h laboratory

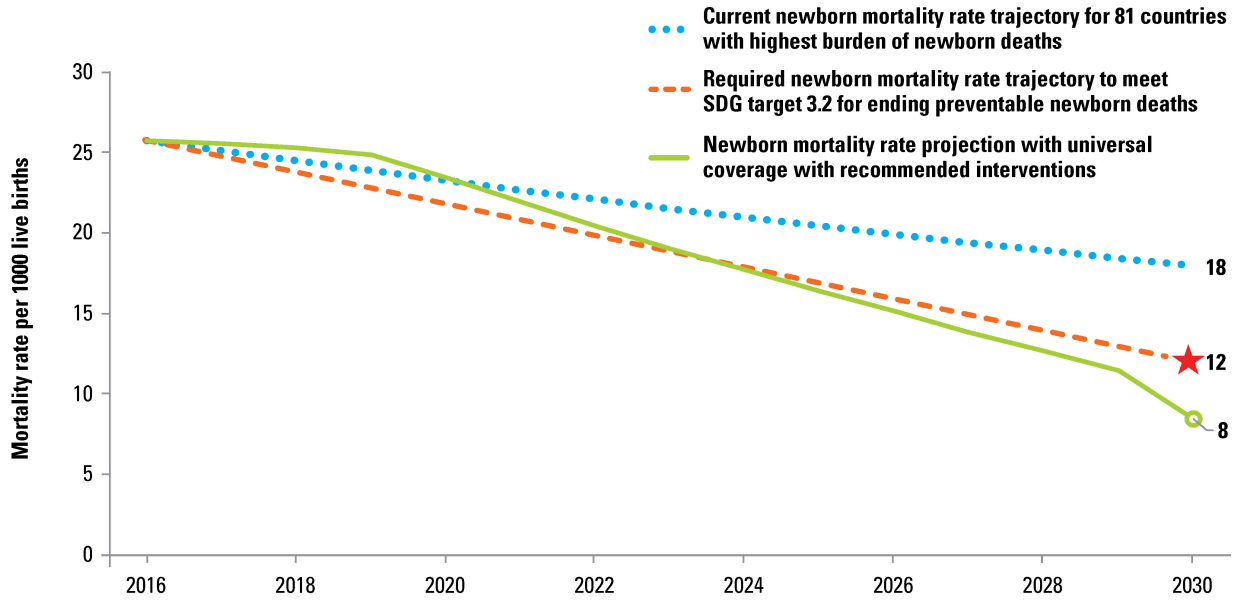
support, and systems for transport and referral.[34] A recent survey of clinicians and programme professionals working in newborn health identified a subset of neonatal interventions or services as 'transitional' between special and intensive care. These included CPAP, seizure management, blood and exchange transfusion, retinopathy screening and treatment for preterm infants, and specialised follow-up for high-risk infants.[41]

Figure 1-5. Levels of inpatient neonatal care, with health system requirements for each level



Source: Moxon et al, 2015.[34] Red text indicates tracer for health system bottleneck analysis.

Figure 1-6. Scenarios to 2030 for 81 high-burden countries: current neonatal mortality rate trajectory; trajectory required to meet SDG target 3.2; and projection if every newborn covered by universal health coverage



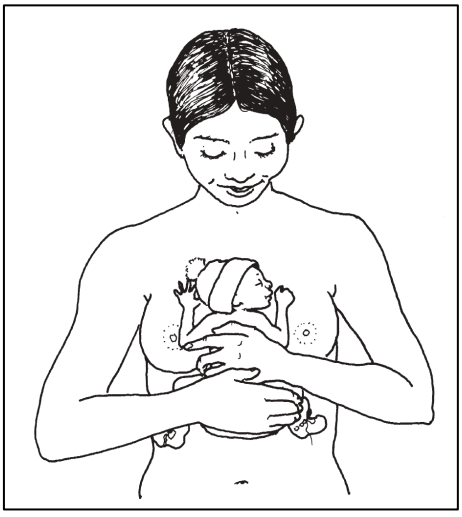
Source: World Health Organisation, 2019.[39]

1.5. Overview of thermal care for preterm and LBW neonates

1.5.1. Kangaroo mother care

KMC is an intervention consisting of early skin-to-skin contact, usually with the mother; promotion of exclusive breastmilk feeding; early hospital discharge; and adequate support and close follow-up at home.[8] Figure 1-7 shows the optimal KMC position with infant upright and skin-to-skin between the mother's breasts.

Figure 1-7. Optimal positioning for kangaroo mother care



Source: World Health Organisation, 2003.[8]

The latest Cochrane review (21 trials) and a meta-analysis (124 studies) demonstrated that KMC among *stable* neonates ≤2000g is associated with decreased mortality,[42,43] sepsis,[42,43] hypothermia,[43] hypoglycaemia,[43] and length of stay (LOS)[42] compared to standard care. World Health Organisation (WHO) guidelines recommend KMC for "routine care of newborns weighing ≤2000g… initiated as soon as newborns are clinically *stable*;"[44] where stability has been defined as vital functions (breathing, circulation) not requiring "continuous medical support and monitoring," and not being "subject to rapid and unexpected deterioration."[8]

1.5.2. Incubator care

Incubators are the standard alternative to KMC for thermal care in preterm and LBW neonates. Due to high purchase cost and poor routine maintenance practices, hospitals in low-resource settings often lack an adequate quantity of functional incubators (Figure 1-8).[45–48] Potential risks associated with incubator care include hypothermia;[49,50] hyperthermia;[51] nosocomial infections related to lack of effective cleaning standards;[52–54] and cross-infection from other neonates when incubators are shared, a common practice in low-resource facilities. Failure of incubators to properly regulate temperature may be related to malfunction (over-heating or under-heating),[51,54–57] loss of electrical supply,[45] poor understanding of set-point regulation,[51] and environmental factors.[55]

Figure 1-8. Incubators in newborn special care units, Iganga District, Uganda

Source of images: Melissa Medvedev, 2016.

1.6. Rationale for thesis

In LMIC settings, provision of high-quality inpatient care for small and sick newborns is often precluded by limited availability of skilled providers, especially nurses, and shortages of essential drugs, supplies, and equipment.[33–36] These health system bottlenecks must be recognised and addressed to accelerate progress in reducing the burden of death and disability following neonatal conditions. Existing scoring systems to quantify neonatal illness severity and mortality risk have primarily been developed for high-income contexts, using laboratory-derived and therapy-derived measures that are typically unavailable (e.g., blood gas, oxygenation index) or observations that are not routinely collected or reliably measurable (e.g., urine output, gestational age) in resource-constrained facilities.[58,59] Assessing individual risk, using a simplified score feasible for LMIC settings, and monitoring facility readiness are imperative to help address the aforementioned health system bottlenecks and promote improved quality of care for small and sick newborns.

WHO guidelines recommend initiation of KMC once newborns are clinically stable.[44] However, the majority of neonatal deaths occur within 48h of birth,[11] *prior to stabilisation*. The only randomised controlled trial (RCT) of KMC initiated before stabilisation, which reported mortality outcomes, was conducted in Ethiopia and enrolled 123 newborns ≤2000g. It reported a 43% reduction in mortality; however, 66% of deaths and the major difference between arms occurred within 12h of birth.[37,60] Further, this trial excluded >50% of eligible newborns, failed to utilise allocation concealment, and had an apparent group imbalance at baseline (favouring KMC),[60] compromising robustness. Analyses adjusting for this imbalance were not presented and outcome data were selectively reported, raising the likelihood of reporting bias.[61] Thus, the effect of KMC initiated before stabilisation remains an unaddressed research priority and a well-designed RCT is warranted to examine mortality impact relative to standard care, particularly in settings where neonatal intensive care is not available.[37,62]

2. Aim and Objectives

2.1. Overall aim

The overall aim of this PhD is to improve risk prediction amongst small and sick newborns and inform the design of a RCT of KMC initiated before stabilisation in a sub-Saharan African context.

2.2. Objectives

1. To develop clinical cascades to evaluate facility readiness for neonatal care, and utilise these to assess 23 health facilities in Kenya and Uganda.
2. To develop and validate a risk score to predict in-hospital neonatal mortality amongst newborns ≤2000g (NMR-2000) within 24h of birth, which is applicable for low-resource settings.
3. To evaluate the feasibility of KMC initiated prior to clinical stabilisation amongst neonates ≤2000g at Jinja Regional Referral Hospital in Uganda.
4. To apply the findings from objectives 1-3 to inform the design of a RCT, which will determine the effect of KMC initiated before stabilisation relative to standard care on mortality within 7 days amongst neonates ≤2000g at four hospitals in Uganda.
5. To synthesise the implications of this thesis for policy, programmes, and research for newborn care in East Africa and beyond.

2.3. Thesis structure

This thesis follows the research paper style, with four of the chapters being papers that have been published in peer-reviewed journals. An overview of the component chapters is provided below. Further details are provided in section 2.4, including related objectives, research themes and questions, and methods.

Chapter 1 provides a background on the global burden of neonatal mortality, mortality in preterm and LBW neonates, neonatal mortality in the sub-Saharan African context, the levels of neonatal inpatient care, and an overview of KMC and incubators for thermal care of preterm and LBW neonates. The rationale for the thesis is included.

Chapter 2 (this chapter) includes the aim, objectives, and details regarding ethical approvals and funding for the work contained within the thesis.

Chapter 3 addresses *Objective 1* and details the development and utilisation of a clinical cascade model to assess the physical readiness of 23 health facilities in Kenya and Uganda to identify and manage common neonatal conditions. Chapter 3 has been published in a peer-reviewed journal (PLoS One).

Chapter 4 addresses *Objective 2*. It describes the development and validation of a risk score practicable for LMIC settings to predict mortality amongst hospitalised newborns ≤2000g within 24h of birth, using datasets from the United Kingdom (UK) and The Gambia. Chapter 4 has been published in a peer-reviewed journal (The Lancet Child and Adolescent Health).

Chapter 5 includes a literature review of the existing evidence regarding KMC, including duration, time of initiation, effect on mortality and other important clinical outcomes, and potential causal pathways for these clinical effects.

Chapter 6 addresses *Objective 3* and describes the findings of a mixed methods study that determined the proportion of admitted neonates meeting proposed instability criteria, assessed the feasibility of providing KMC to unstable neonates, and evaluated the acceptability of this intervention to parents and providers at Jinja Regional Referral Hospital in Uganda. Chapter 6 has been published in a peer-reviewed journal (Journal of Global Health).

Chapter 7 addresses *Objective 4* and provides a detailed overview of the protocol for a four-centre, open-label, individually randomised, superiority trial, which aims to determine the effect of KMC initiated before stabilisation relative to standard care on mortality within 7 days amongst neonates ≤2000g in Uganda. Chapter 7 has been published in a peer-reviewed journal (Trials).

Chapters 8 and 9 address *Objective 5*. Chapter 8 draws together lessons learnt from Objectives 1 through 4 and provides an overall summary of the work, including implications. Chapter 9 provides recommendations for policy, programmes, and research.

2.4. Table of overview of thesis chapters, objectives, methods, and papers

Table 2-1. Overview of thesis chapters, objectives, methods, and papers

Chapter number and title		Objective	Sub-objectives	Methods	Paper
1	Background and rationale	To provide context and describe rationale for this PhD thesis	Describe global burden of neonatal mortality, including sub-Saharan Africa, Kenya, and Uganda Provide overview of the levels of neonatal inpatient care Provide overview of KMC and incubator care for thermal support	Targeted literature review	
2	Aim and objectives				
3	Clinical cascades as a novel way to assess physical readiness of facilities for the care of small and sick neonates in Kenya and Uganda	**Objective 1:** To develop clinical cascades to evaluate facility readiness for neonatal care and utilise these to assess 23 health facilities in Kenya and Uganda	1.1 Develop clinical cascades for six common neonatal conditions 1.2 Utilise the clinical cascades to assess 23 health facilities in Kenya and Uganda 1.3 Determine changes in resources availability over time by facility	Review of WHO clinical guidelines Estimation of mean readiness, readiness loss McNemar's test	Clinical cascades as a novel way to assess physical readiness of facilities for the care of small and sick neonates in Kenya and Uganda, published in *PLoS One*[63]
4	Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000g or less: an analysis using data from the UK and The Gambia	**Objective 2:** To develop and validate a risk score feasible for low-resource settings to predict in-hospital mortality amongst newborns ≤2000g within 24h of birth	2.1 Evaluate existing neonatal illness severity and mortality risk scores to select candidate variables 2.2 Develop and validate a score to predict in-hospital neonatal mortality risk amongst newborns ≤2000g (NMR-2000) 2.3 Compare the performance of the novel score (NMR-2000) with that of an existing score (CRIB-II)	Literature review Logistic regression, prediction model Comparison of areas under the receiver operating characteristic curves	Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000g or less: an analysis using data from the UK and The Gambia, published in *The Lancet Child and Adolescent Health*[64]

***Table A1-1 provides a detailed overview of my role in each component of this thesis**

Chapter number and title		Objective	Sub-objectives	Methods	Paper
5	Current evidence regarding duration, timing, clinical impact, and causal pathways for clinical effects of kangaroo mother care: literature review	To review existing evidence regarding KMC, including duration, time of initiation, effect on mortality and other clinical outcomes, and potential causal pathways for these effects		Literature review	
6	Kangaroo Mother Care for clinically unstable neonates: is it feasible at a hospital in Uganda?	**Objective 3:** To evaluate the feasibility of KMC initiated prior to stabilisation amongst neonates ≤2000g at Jinja Hospital in Uganda	3.1 Determine the proportion of admitted neonates meeting proposed instability criteria 3.2 Assess the feasibility of monitoring and providing interventions to unstable neonates ≤2000g in the KMC position 3.3 Evaluate the acceptability of KMC for unstable neonates ≤2000g to parents and healthcare providers	Chart review Estimation of KMC duration and number of concurrent therapies Semi-structured interviews, thematic content analysis	Kangaroo Mother Care for clinically unstable neonates: is it feasible at a hospital in Uganda?, published in *Journal of Global Health*[65]
7	Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa (OMWaNA): protocol for a randomised controlled trial to examine mortality impact in Uganda	**Objective 4:** To apply the findings of objectives 1-3 to inform the design of a RCT, which will determine the effect of KMC initiated before stabilisation relative to standard care on mortality within 7 days amongst neonates ≤2000g at four hospitals in Uganda	Provide a detailed overview of the protocol for a four-centre, open-label, individually randomised, superiority trial that aims to determine the effect of KMC initiated before stabilisation relative to standard care on mortality within 7 days amongst neonates ≤2000g in Uganda		Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa (OMWaNA): protocol for a randomised controlled trial to examine mortality impact in Uganda, published in *Trials*[66]
8	Discussion and implications	To discuss the main findings of the thesis and outline key implications	Discuss overall strengths and limitations		
9	Recommendations and conclusion	**Objective 5:** To describe the implications of these findings for policy, programmes, and research in East Africa and beyond	Summarise recommendations for policy, programmes, and future research		

2.5. Ethics

Facility readiness assessment work in Kenya and Uganda (chapter 3) was covered as part of the broader research efforts of the University of California San Francisco (UCSF) Preterm Birth Initiative-East Africa, which received approval from the ethics committees of UCSF, Makerere University, the Uganda National Council for Science and Technology (UNCST), and the Kenya Medical Research Institute. Where required, ethical approval for other work included in this thesis was obtained from the Research Ethics Committee (REC) of the London School of Hygiene and Tropical Medicine (LSHTM). Ethical approval for risk score development and validation (chapter 4) was also obtained from the North West–Preston REC, the UK Health Research Authority, and the REC of the Gambian Government/Medical Research Council Unit The Gambia at LSHTM. The KMC feasibility study (chapter 6) was additionally approved by the RECs of Makerere University and UNCST, and the OMWaNA trial (chapter 7) by the RECs of the Uganda Virus Research Institute and UNCST. All approval letters are included in the annex. Further details regarding ethical considerations, including informed consent, are described in individual chapters.

2.6. Funding

Funding for PhD tuition was received from the UCSF Preterm Birth Initiative as part of a postdoctoral fellowship at UCSF from 2015 to 2017. Costs of travelling to London for PhD work were supported by the UCSF Preterm Birth Initiative fellowship award and a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (Grant ID: K23HD092611). Work on the facility readiness cascades and the cost of using data from the UK National Neonatal Research Database for the mortality risk score work were funded by the Bill & Melinda Gates Foundation through a grant to the UCSF Preterm Birth Initiative (Grant ID: OPP 1107312). Work on the risk score was supported by a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Grant ID: K23HD092611) awarded to Melissa Medvedev and a Wellcome Trust Fellowship (Grant ID: 2000116) awarded to Helen Brotherton. The KMC feasibility study was funded by the UCSF Preterm Birth Initiative (as part of postdoctoral fellowship award) and the Thrasher Research Fund (Grant ID: 13388). The OMWaNA trial is funded by the Joint Global Health Trials scheme of the Department of Health and Social Care, Department for International Development, Medical Research Council, and The Wellcome Trust (Grant ID: MR/S004971/1) awarded to Joy Lawn. Funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Grant ID: K23HD092611) also supported my work on the trial.

3. Clinical cascades as a novel way to assess physical readiness of facilities for the care of small and sick neonates in Kenya and Uganda (Paper A)

3.1. Scope of this chapter

Chapter 3 presents the first research paper entitled, "Clinical cascades as a novel way to assess physical readiness of facilities for the care of small and sick neonates in Kenya and Uganda." This paper describes an innovative approach utilising clinical cascades for six common neonatal conditions/emergencies to assess facility readiness across three stages of care (identification, treatment, monitoring-modifying treatment), which is employed to assess 23 health facilities in Kenya and Uganda. While the focus of this paper is on physical readiness for neonatal inpatient care more broadly, this work is included as the first paper of this PhD to illustrate the current context for such care in East Africa and to demonstrate the facility-level resource issues that must be recognised and addressed to facilitate safe and effective provision of evidence-based interventions in this vulnerable patient population.

This work was published in *PLoS One* as an open access article in November 2018. See Appendix A.3.1 for the copyright.

3.2. List of figures

3.3. List of tables

3.4. Citation

Morgan M, Spindler H, Nambuya H, Nalwa G, Namazzi G, Waiswa P, Otieno P, Cranmer J, Walker D. **Clinical cascades as a novel way to assess physical readiness of facilities for the care of small and sick neonates in Kenya and Uganda**. *PLoS One* 2018; 13(11):e0207156. doi: 10.1371/journal.pone.0207156.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	131393	**Title**	Dr
First Name(s)	Melissa Morgan		
Surname/Family Name	Medvedev		
Thesis Title	Informing the design of a trial of kangaroo mother care initiated before stabilisation amongst small and sick newborns in a sub-Saharan African context using mixed methods		
Primary Supervisor	Elizabeth Allen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PLoS One as: Morgan MC, Spindler H, Nambuya H, Nalwa GM, Namazzi G, Waiswa P, Otieno P, Cranmer J, Walker DM. Clinical cascades as a novel way to assess physical readiness of facilities for the care of small and sick neonates in Kenya and Uganda. PLoS One. 2018; 13(11): e0207156. doi: 10.1371/journal.pone.0207156.		
When was the work published?	November 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not applicable		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised the paper with Prof Dilys Walker and Dr John Cranmer. I developed the neonatal clinical cascades with Drs Harriet Nambuya, Grace Nalwa, and Gertrude Namazzi. I designed the analytic plan, with input from Dr John Cranmer and Ms Hilary Spindler, and I conducted all analyses. I wrote the first draft of the manuscript and prepared all subsequent revisions with consideration of comments from co-authors. See Annex A.1. for full details.

SECTION E

Student Signature	Melissa Medvedev
Date	10th October 2019

Supervisor Signature	Elizabeth Allen
Date	11/10/19

PLOS ONE

RESEARCH ARTICLE

Clinical cascades as a novel way to assess physical readiness of facilities for the care of small and sick neonates in Kenya and Uganda

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Abstract

Background

Globally, there were 2.7 million neonatal deaths in 2015. Significant mortality reduction could be achieved by improving care in low- and middle-income countries (LMIC), where the majority of deaths occur. Determining the physical readiness of facilities to identify and manage complications is an essential component of strategies to reduce neonatal mortality.

Methods

We developed clinical cascades for 6 common neonatal conditions then utilized these to assess 23 health facilities in Kenya and Uganda at 2 time-points in 2016 and 2017. We calculated changes in resource availability over time by facility using McNemar's test. We estimated mean readiness and loss of readiness for the 6 conditions and 3 stages of care (identification, treatment, monitoring-modifying treatment). We estimated overall mean readiness and readiness loss across all conditions and stages. Finally, we compared readiness of facilities with a newborn special care unit (NSCU) to those without using the two-sample test of proportions.

Results

The cascade model estimated mean readiness of 26.3–26.6% across the 3 stages for all conditions. Mean readiness ranged from 11.6% (respiratory distress-apnea) to 47.8% (essential newborn care) across both time-points. The model estimated overall mean

Competing interests: The authors have declared that no competing interests exist.

readiness loss of 30.4–31.9%. There was mild to moderate variability in the timing of readiness loss, with the majority occurring in the identification stage. Overall mean readiness was higher among facilities with a NSCU (36.8%) compared to those without (20.0%).

Conclusion

The cascade model provides a novel approach to quantitatively assess physical readiness for neonatal care. Among 23 facilities in Kenya and Uganda, we identified a consistent pattern of 30–32% readiness loss across cascades and stages. This aggregate measure could be used to monitor and compare readiness at the facility-, health system-, or national-level. Estimates of readiness and loss of readiness may help guide strategies to improve care, prioritize resources, and promote neonatal survival in LMICs.

Introduction

Globally, there were 2.7 million neonatal deaths in 2015 [1]. The leading causes were preterm birth, defined as birth before 37 completed weeks of gestation (16%), intrapartum-related events (11%), and sepsis or meningitis (7%) [1]. Deaths in the neonatal period are responsible for 45% of all deaths in children under age 5, with preterm birth being the leading cause [1]. Major mortality reduction could be achieved by improving care in low- and middle-income countries (LMIC) [2–5]. Within the neonatal period, 36% of deaths occur on the day of birth and 73% occur in early neonatal period, defined as the first 7 days [2]. Between 1980 and 2015, early neonatal mortality has decreased more slowly than all other age-categories of under-5 mortality [6]. Thus, the immediate postnatal and early neonatal periods represent critical windows of opportunity to improve neonatal survival globally.

Facility-based care of small and sick neonates, including neonatal resuscitation, kangaroo mother care (KMC), intravenous (IV) fluids, feeding support, oxygen, antibiotics, and phototherapy, could avert an estimated 580,000 neonatal deaths annually [7]. Estimates suggest that provision of available interventions in facilities could decrease prematurity, intrapartum, and infection-related causes of neonatal mortality by 58%, 79%, and 84%, respectively [7]. Conversely, some of these interventions also carry a risk of harm when administered by inadequately trained staff or without proper equipment. For example, provision of oxygen therapy in the absence of pulse oximetry monitoring increases the risk of retinopathy and subsequent visual impairment in preterm neonates [8,9]. Although an estimated 72% of deliveries globally occurred in facilities from 2012 to 2017 [10], lack of access to delivery and postnatal care remains a challenge in LMICs [11–13]. Further, essential interventions are not successfully implemented in many LMICs due to an array of underlying constraints, including shortages of skilled providers, inadequate funding, poor distribution of newborn care services, and weak referral systems [14]. To better understand such barriers and ultimately address the functionality of a health system as a whole, facility-level capacity limitations must first be identified.

However, analyzing facility capacity has been an ongoing focus of public health for decades and competing theories exist on how to best approach such an analysis. To develop and further standardize an approach, the United Nations Children's Fund (UNICEF) and the World Health Organization (WHO) published guidelines describing "signal functions" related to facility readiness for provision of Essential Obstetric Care (EOC) [15]. These signal functions represent a selection of key interventions used to treat obstetric complications, which classify and monitor the level of care (basic or comprehensive) being provided by a facility, rather than

listing all EOC services that should be provided [15]. In 2009, EOC was replaced by Emergency Obstetric and Newborn Care (EmONC), and the list of signal functions was expanded to include neonatal resuscitation (with a bag and mask) at facilities providing basic or comprehensive levels of care [16]. Availability, use, and quality of EmONC have been suggested as pragmatic indicators to monitor and evaluate the progress of health systems towards reducing maternal and neonatal mortality [16–21], yet there have been few attempts to develop additional signal functions for neonates. One study evaluated indicators for the quality of pediatric hospital care in LMICs and found broad support among experts for several newborn indictors, including availability of tetracycline, vitamin K, parenteral antibiotics, and drugs for the prevention of mother-to-child transmission (PMTCT) of HIV [22]. In 2012, new signal functions were proposed for routine and emergency newborn care, including KMC, IV fluids, cup feeding, oxygen, antibiotics, and PMTCT [18]; however, these have not been widely adopted globally. A recent study delineated over 600 structural characteristics, including infrastructure, equipment, drugs, providers and guidelines, for facility readiness to deliver care for small and sick newborns, and work is currently underway to finalise recommendations for newborn signal functions [23].

Notably, the signal function approach is subject to limitations and recommendations for alternative approaches have led researchers to the rethink the analysis of capacity. Potter and Brough emphasized that the key components of a functioning health system (i.e., facility/staff, skills, tools) are hierarchical in nature, and depend greatly upon the availability and functionality of each other [24,25]. Applied to a clinical context, a medical intervention can only be effectively administered if the necessary infrastructure, staff, and tools are first in place. Through precise identification of resource shortages, capacity needs can be tied to specific gaps found within each step of the hierarchy [24]. The HIV treatment cascade was developed as a tool to identify gaps in care delivery and to prioritize resources with the goal of improving public health [26–28]. At each step of the cascade (e.g., diagnosis, linkage to care), patients may be lost to follow-up and, as a result, fail to access or benefit from available health interventions. The cascade approach has subsequently been applied to other areas of public health, including PMTCT [29], hepatitis C [30], diabetes [31], hypertension [32] and, most recently, emergency obstetric care [33]. The latter introduced the clinical cascade model, which highlights the fact that multiple resources are required sequentially or simultaneously in order to provide real-time patient care [33]. For example, a provider can effectively treat a sick neonate requiring immediate care only when all resources needed to identify and treat the underlying condition are simultaneously present in the facility. In the obstetric cascade study, Cranmer and colleagues assessed 44 primary care facilities in Kakamega County, Kenya and found that 39–100% had the resources required for identification, 7–57% had resources for treatment, and 0–2% had resources to monitor or modify treatment across five common maternal emergencies [33].

Informed by Potter and Brough's capacity pyramid and based on the obstetric emergency cascade [24,33], we aimed i) to develop clinical cascades to evaluate facility readiness to care for small, sick neonates and ii) to utilize these to assess 23 health facilities in Kenya and Uganda.

Methods

Study setting

In Kenya and Uganda, annual neonatal mortality rates have slowly decreased over the last decade, but remain high at 21 and 20 deaths per 1,000 live births, respectively (2017) [34]. Estimated preterm birth rates are 12% for Kenya and 14% for Uganda [35]. We conducted facility assessments at 23 health facilities- 17 in Migori County, Kenya and 6 in Busoga Region,

Uganda. In Kenya, facilities included 1 county referral hospital, 10 sub-county hospitals, 2 mission hospitals, and 4 health centers. In Uganda, facilities included 1 regional referral hospital, 3 district hospitals, and 2 mission/private non-for-profit (PNFP) hospitals. All of the facilities were intervention sites for a larger Preterm Birth Initiative study focused on data strengthening and provider skills training.

Study procedures

Cascade development. Using the WHO Guidelines for the Management of Common Childhood Illnesses [36], researchers (MM, DW) developed a list of evidence-based treatments for 6 common neonatal conditions/emergencies: essential (routine) newborn care (for all newborns); neonatal resuscitation; poor feeding-hypothermia; respiratory distress-apnea of prematurity; infection-convulsions; and jaundice. We also reviewed local guidelines, which were available for a subset of these conditions, and found them to be congruent with the WHO Guidelines [36]. Researchers (MM, HN, GMN, GN, PW, PO, DW) then developed and refined lists of essential supplies, including drugs, needed at each stage of the facility readiness cascades: identification of the condition/emergency (stage 1), treatment (stage 2), and monitoring and modifying treatment as clinically indicated (stage 3). Supplies considered infeasible for routine use in LMIC settings [IV epinephrine; X-ray machine; laboratory testing supplies (e.g., for bacterial culture, complete blood count, blood type, Coombs test); supplies for lumbar puncture and exchange transfusion)] were not included in the final cascades. Readiness was defined by the presence of all required supplies/drugs for each clinical cascade and stage of care, and overall across the 3 stages for all 6 conditions. Within each clinical cascade, readiness for individual supplies required the simultaneous presence of all preceding supplies in that cascade. Within each stage, individual supplies were organized sequentially in the order in which they would be required to to provide real-time care.

Facility assessments. We conducted facility assessments at two time-points, approximately nine months apart, in 2016 and 2017, to determine if any changes in supply availability occurred over time. Further, as all of the facilities were intervention sites for a larger study, it was important to monitor supply availability in order to establish any potential impacts on the ongoing project. All assessments were conducted by in-country project staff with a background in either clinical care or monitoring and evaluation. Data collectors confirmed the presence and functionality of items located in neonatal units, labor rooms, and maternity wards through visual identification. Data collectors verbally inquired with a pharmacist or other pharmacy staff member to determine the availability of drugs. Staff recorded the presence or absence of items during facility assessments using a mobile application tool on the OpenDataKit platform (https://opendatakit.org). Using this tool, data collectors could also record any additional notes of interest.

Statistical analysis

We described facility characteristics and neonatal care variables with standard descriptive statistics, including mean, standard deviation (SD), median, interquartile range (IQR), frequency, and proportion. Point estimates for resource availability across all facilities at each time-point were summarized as counts and proportions. Changes in resource availability over time by facility were calculated using McNemar's test. Since the dataset had fewer than 100 observations or data were not normally distributed, non-parametric statistics with two-sided tests of significance were used for all analyses. Loss of readiness was calculated by subtracting readiness at a given stage from readiness in the preceding stage. In the identification stage, readiness loss was calculated by subtracting readiness from 100%. Means were used to estimate overall

readiness and loss of readiness because these measures were based on few observations, thus medians would not accurately capture the range of observations. Variability was summarized using the absolute range and SD since resource availability varied greatly. Readiness loss between stages was quantified with percentages. Since resource requirements differ based upon the expected level of care provision [8,18,37], we estimated readiness for each clinical cascade and stage of care by facility level as well as by country. In the sub-analysis of health clinics, we excluded items that are not expected to be available at this level of facility [37]. Further, we compared the readiness of facilities with a functional newborn special care unit (NSCU) to those without using the two-sample test of proportions. All statistical analyses were carried out using Stata 15.1 (StataCorp LP, College Station, Texas, United States of America).

Ethics

We obtained ethical approval from the Institutional Review Boards of Makerere University, the Uganda National Council for Science and Technology, the Kenya Medical Research Institute, and the University of California San Francisco. The facility assessment data did not require individual informed consent.

Results

Facility characteristics

Among the 23 facilities assessed, the median monthly delivery volume was 52 (IQR: 29–160; Table 1). Delivery volumes were highest among facilities at the regional, district, or county level (median: 212, IQR: 188–427) and lowest among facilities at the health center level (median: 25, IQR: 21–30). Eight (35%) facilities had a functional NSCU, with a median monthly admission volume of 35 (IQR: 24–108; Table 1). Notably, 6 (100%) of Ugandan facilities had a functional NSCU relative to only 2 (12%) of Kenyan facilities.

Across all 23 facilities, there were a median of 0 pediatricians, 1 general doctor, 0 clinical officers, and 8 nurse-midwives working in neonatal care (Table 1). Pediatricians were only available at 2 (9%) facilities, both of which were regional- or district-level hospitals in Uganda. All 6 Ugandan facilities had $\geq$1 general doctor working in neonatal care. Among the 17 Kenyan facilities, 6 had $\geq$1 general doctor, 6 had $\geq$1 clinical officer, and 5 had only nurse midwives working in neonatal care.

Neonatal care resource availability

Across the 2 time-points, there was wide variability in the availability of durable goods (range: 4–91%; S1 Table) and consumable supplies (range: 17–96%; S2 Table). Availability of clean cloth or towels (-34.8%, p = 0.0325), resuscitation area with warmer (-22%, p = 0.0253), and glucometers (-30%, p = 0.0082) by facility significantly decreased over time (S1 Table). No significant changes in the availability of consumable supplies by facility were identified (S2 Table). Wide variability also existed for newborn special care tracer items [8], including oxygen (78%), pulse oximeters (22–44%), IV fluids [Ringers lactate or half normal saline/5% dextrose (91%)], and nasogastric tubes (57%; S1 and S2 Tables). The majority of facilities had dextrose (78–96%) and aminophylline (78–91%; S2 Table). A much lower proportion stocked calcium gluconate (39%) and ceftriaxone or cefotaxime (57–65%; S2 Table).

Clinical cascade estimates of neonatal care readiness

Overall, the cascade model estimated mean readiness of 27% (SD: 23) in 2016 and 26% (SD: 28) in 2017 across the 3 stages of care for all 6 conditions. In 2016, mean readiness was 51%

Table 1. Facility characteristics by facility level.

	All facilities, N = 23	Regional/district/ county level, n = 5	Mission/PNFP level, n = 4	Sub-county level, n = 10	Health center level, n = 4
Delivery and newborn unit admission volume					
Monthly delivery volume, median (IQR)[a]	52 (29–160)	212 (188–427)	108 (61–145)	44 (27–63)	25 (21–30)
Functional newborn special care unit (NSCU), n (%)[b]	8 (35)	5 (100)	3 (75)	0 (0)	0 (0)
Monthly NSCU admissions, median (IQR)[c]	35 (24–108)[d]	39 (35–108)	28 (24–32)[e]	N/A	N/A
Human resources for neonatal care					
Pediatrician, median (IQR)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
Any pediatrician, n (%)	2 (9)	2 (40)	0 (0)	0 (0)	0 (0)
General doctor, median (IQR)	1 (0–1)	1 (1–1)	3 (2–4)	0 (0–1)	0 (0–0)
Any general doctor, n (%)	12 (52)	5 (100)	4 (100)	3 (30)	0 (0.0)
Clinical officer, median (IQR)	0 (0–1)	0 (0–0)	0 (0–0)	1 (0–1)	2 (1–3)
Any clinical officer, n (%)	6 (26)	0 (0)	0 (0)	3 (30)	3 (75)
Nurse midwife, median (IQR)	8 (6–12)	14 (14–15)	10 (9–12)	7 (5–8)	6 (5–8)
Any nurse-midwife, n (%)	23 (100)	5 (100)	4 (100)	10 (100)	4 (100)

[a] Calculated as the number of deliveries per month, averaged over 12 months (September 2016 to August 2017), by facility level.

[b] NSCUs are expected to provide feeding support for small and sick infants (including IV fluids and nasogastric tubes); infection prevention and management (including antibiotics); oxygen therapy (with pulse oximetry); phototherapy; incubators or radiant warmers; and space for neonatal resuscitation and KMC. Tertiary facilities offering neonatal intensive care are expected to additionally provide CPAP, mechanical ventilation, surfactant therapy, and 24-hour laboratory support [8].

[c] Calculated as the number of admissions to NSCU per month, averaged over 12 months (September 2016 to August 2017), by facility level.

[d] Figure reflects data from all 6 Ugandan facilities and 1 of the 2 Kenyan facilities with a functional NSCU; these data are not routinely collected in Kenyan facilities below the county level.

[e] Figure reflects data from the 2 Ugandan facilities; this data is not routinely collected in Kenyan facilities below the county level.

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(SD: 17) in the identification stage, 20% (SD: 12) in the treatment stage, and 9% (SD: 15) in the monitoring-modifying stage across the 6 cascades. In 2017, mean readiness was 57% (SD: 24) in the identification stage, 17% (SD: 14) in the treatment stage, and 4% (SD: 6) in the monitoring-modifying stage. Across both time-points, mean readiness by cascade ranged from 12% (respiratory distress-apnea) to 48% (essential newborn care; Tables 2 and 3; Figs 1 and 2).

In 2017, 14 of 23 facilities (61%) had the resources necessary to identify a non-vigorous neonate requiring resuscitation, including water and soap (or hand disinfectant), stethoscope, and disposable gloves (Table 2; Fig 3). Of those, 12 (52%) had a resuscitation area with heat lamp,

Table 2. Neonatal care readiness for the essential newborn care, neonatal resuscitation, and poor feeding-hypothermia clinical cascades, 2016 and 2017 (N = 23 facilities).

	Stage	Item	2016 n (%)[a]	2017 n (%)[a]
Essential Newborn Care	**Identify**	Water and soap, or hand disinfectant	18 (78)	19 (83)
	Treat	Clean blade / cord ties[b][38]	18 (78)	17 (74)
		Vitamin K (IM)	10 (44)	8 (35)
		Tetracycline eye ointment	9 (39)	8 (35)
		PMTCT in line with national policy[c]		
	Monitor-Modify	Newborn weighing scale	9 (39)	6 (26)
		Guidelines: referral of sick newborns	9 (39)	3 (13)

(*Continued*)

Table 2. (Continued)

	Stage	Item	2016 n (%)[a]	2017 n (%)[a]
Neonatal Resuscitation	**Identify**	Water and soap, or hand disinfectant	18 (78)	19 (83)
		Stethoscope	13 (57)	17 (74)
		Disposable gloves	11 (48)	14 (61)
	Treat	Resuscitation area with heat lamp	11 (48)	12 (52)
		Ventilation bag	9 (39)	10 (44)
		Mask–term / preterm size[d]	7 (30)	8 (35)
		Suction device	7 (30)	8 (35)
	Monitor-Modify	Neonatal resuscitation algorithm	3 (13)	5 (22)
		Thermometer	2 (9)	5 (22)
		Pulse oximeter with probe	2 (9)	3 (13)
		Guidelines: referral of sick newborns	2 (9)	1 (4)
Poor Feeding- Hypothermia	**Identify**	Water and soap, or hand disinfectant	18 (78)	19 (83)
		Newborn weighing scale	18 (78)	17 (74)
		Thermometer	17 (74)	17 (74)
		Tape measure	12 (52)	15 (65)
	Treat	Incubator or radiant warmer[e] [39]	9 (39)	11 (48)
		KMC bed or chair[f] [40]	3 (13)	6 (26)
		IV cannula sets	3 (13)	6 (26)
		IV bags or tubing	2 (9)	1 (4)
		Dextrose (IV)	2 (9)	1 (4)
		Nasogastric tube (neonatal size)	2 (9)	1 (4)
		Syringes / cups	2 (9)	1 (4)
	Monitor-Modify	Lancets (neonatal or infant size)	1 (4)	1 (4)
		Glucose test strips	1 (4)	1 (4)
		Glucometer	0	0
		Postnatal gestational age assessment tool[g]	0	0
		Preterm infant feeding guidelines	0	0
		Ringers lactate (in 10% dextrose) or half normal saline/ 5% dextrose[h] [41]	0	0
		Guidelines: referral of sick newborns	0	0

[a] For each successive item in a clinical cascade, readiness requires the simultaneous presence of all preceding items in that cascade.

[b] Clean, dry cord care is recommended for all neonates born in health facilities. Chlorhexidine 4% is recommended only for neonates born at home in settings with high neonatal mortality (NMR ≥30), or to replace application of a harmful traditional substance to the umbilical cord (e.g., cow dung), thus it was not included.

[c] In settings with high HIV prevalence, PMTCT is required for neonates born to mothers with positive HIV test (not assessed in this study).

[d] Term (size 1) masks are required for normal-weight infants and preterm (size 0) masks are required for infants weighing <2500 grams (g) [36]. In this study, the presence of term or preterm size masks was assessed in facilities.

[e] An incubator or radiant warmer is required for thermal care of neonates weighing ≤2000g who are: 1) clinically unstable, or 2) clinically stable, but mother/other caregiver is not able/available to provide KMC.

[f] A clean cloth (may be brought by the mother), sized approximately 1 square meter, may be folded and securely tied to function as a KMC support wrap/binder. This may later be replaced by a carrying pouch of the mother's choice.

[g] Ballard, Dubowitz, or simplified postnatal gestational age assessment tool is required to calculate gestational age when last menstrual period (LMP) is unavailable, unreliable, or incongruent with appearance.

[h] Ringers lactate (added to 10% dextrose in an appropriate ratio, e.g., 1:4) or half normal saline/5% dextrose is required for fluid maintenance in neonates unable to tolerate enteral feeds after the first 2 days.

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10 (44%) had a ventilation bag, and 8 (35%) had an appropriately-sized mask and suction device. Only 1 facility (4%) also had guidelines for referral of sick newborns, which should be

present in all facilities offering newborn care as this is essential to help providers identify neonates who require a higher level of care (Table 2; Fig 3). In 2016, 12 facilities (52%) had water and soap (or disinfectant), stethoscopes, and thermometers for identifying neonatal infections (Table 3; Fig 4). Only 3 (13%) additionally had supplies to dose and administer parenteral antibiotics (IV cannula sets, IV bags or tubing, and weighing scale). Although 87% of facilities had ampicillin (or penicillin) and 78% had gentamicin (S2 Table), far fewer had the resources to identify infections and accurately administer first-line antibiotics (13% stage 2 readiness; Table 3; Figs 2 and 4).

Clinical cascade estimates of neonatal care readiness by facility type and by country

Among the 5 regional/district/county level facilities, the cascade model estimated mean readiness of 43% (SD: 32) in 2016 and 29% (SD: 28) in 2017 across all stages and conditions (S3 Table). Overall mean readiness was 38% (SD: 31) in 2016 and 44% (SD: 37) in 2017 at the 4

Table 3. Neonatal care readiness for the respiratory distress-apnea, infection-convulsions, and jaundice clinical cascades, 2016 and 2017 (N = 23 facilities).

	Stage	Item	2016 n (%)[a]	2017 n (%)[a]
Respiratory Distress-Apnea	**Identify**	Water and soap, or hand disinfectant	18 (78)	19 (83)
		Stethoscope	13 (57)	17 (74)
		Pulse oximeter with probe	6 (26)	4 (17)
	Treat	Oxygen canister or concentrator	6 (26)	4 (17)
		Oxygen tubing	4 (17)	4 (17)
		Nasal cannula (neonatal size)	4 (17)	4 (17)
		Aminophylline or caffeine citrate[b]	4 (17)	3 (13)
		Ventilation bag	4 (17)	2 (9)
		Mask—term / preterm size[c]	4 (17)	2 (9)
		Suction	4 (17)	2 (9)
	Monitor-Modify	Guidelines: oxygen therapy[d]	2 (9)	0
		Guidelines: apnea of prematurity	0	0
		Continuous positive airway pressure (CPAP) device[e]	0	0
		Guidelines: referral of sick newborns	0	0
Infection-Convulsions	**Identify**	Water and soap, or hand disinfectant	18 (78)	19 (83)
		Stethoscope	13 (57)	17 (74)
		Thermometer	12 (52)	17 (74)
	Treat	IV cannula sets	9 (39)	10 (44)
		IV bags or tubing	3 (13)	3 (13)
		Newborn weighing scale[f]	3 (13)	3 (13)
		Ampicillin or penicillin (IV)	3 (13)	3 (13)
		Gentamicin (IV)	3 (13)	3 (13)
	Monitor-Modify	Guidelines: neonatal sepsis	0	2 (9)
		Lancets (neonatal or infant size)	0	2 (9)
		Glucose test strips	0	2 (9)
		Glucometer	0	0
		Dextrose (IV)	0	0
		Ceftriaxone or cefotaxime[g]	0	0
		Phenobarbital (IV)[h]		
		Calcium gluconate (IV)[h]	0	0
		Guidelines: referral of sick newborns	0	0

(*Continued*)

Table 3. (Continued)

	Stage	Item	2016 n (%)[a]	2017 n (%)[a]
Jaundice	**Identify**	Water and soap, or hand disinfectant	18 (78)	19 (83)
		Lancets (neonatal or infant size)	11 (48)	10 (44)
		Serum bilirubin measurement or bilirubin test strips[i] [42,43]		
	Treat	Phototherapy unit	3 (13)	2 (9)
		Incubator or radiant warmer[j]	3 (13)	2 (9)
	Monitor-Modify	Guidelines: neonatal jaundice[k]		
		Postnatal gestational age assessment tool[k]	1 (4)	2 (9)
		Newborn weighing scale[l]	1 (4)	2 (9)
		Guidelines: referral of sick newborns	1 (4)	2 (9)

[a] For each successive item in a clinical cascade, readiness requires the simultaneous presence of all preceding items in that cascade.

[b] Caffeine citrate (preferred) or aminophylline is required to help prevent and treat apnea in preterm infants.

[c] Term (size 1) masks are required for normal-weight infants and preterm (size 0) masks are required for infants weighing <2500g [36]. In this study, the presence of term or preterm size masks was assessed in facilities.

[d] Oxygen therapy guidelines are needed to help providers modify oxygen therapy based on oxygen saturation and clinical signs.

[e] CPAP is required to provide respiratory support to infants with severe respiratory distress (in secondary/referral-level facilities).

[f] A weighing scale is required for accurate dosing of antibiotics and other medications.

[g] Ceftriaxone or cefotaxime is required as a second-line therapy for meningitis and other severe infections not responding to initial antibiotics within 2–3 days. Ceftriaxone is also used as a first-line therapy with tetracycline eye ointment (in Essential Newborn Care cascade) for ophthalmia neonatorum.

[h] Phenobarbital is required to treat infants who are having convulsions (not assessed in this study). In addition, measurement of serum calcium should be considered (in facilities with laboratory capacity), with calcium gluconate 10% administered for treatment of hypocalcemia.

[i] Bilirubin should be measured in infants with suspected hyperbilirubinemia. Serum bilirubin measurement is preferred (in facilities with laboratory capacity). Rapid bilirubin tests may be used in facilities lacking laboratory capacity (not assessed in this study).

[j] An incubator or radiant warmer is required for thermal care of neonates weighing ≤2000g while receiving phototherapy.

[k] Guidelines are needed to help providers assess risk of severe hyperbilirubinemia and determine treatment threshold (not assessed in this study). Ballard, Dubowitz, or other gestational age assessment tool is required to calculate gestational age (when LMP is unavailable, unreliable, or incongruent with appearance) for use in determining severe hyperbilirubinemia risk and treatment threshold.

[l] A weighing scale is required to monitor for evidence of dehydration during phototherapy.

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mission/PNFP facilities (S3 Table). Comparatively, overall readiness was lower at the 10 sub-county level facilities [2016: mean 16 (SD: 20); 2017: mean 23 (SD: 30)] and the 4 health centers [2016: mean 19 (SD: 32); 2017: mean 27 (SD: 19); S3 Table]. Among the 17 Kenyan facilities, overall mean readiness was 23% (SD: 23) in 2016 and 22% (SD: 28) in 2017 (S4 Table). Overall mean readiness was increased at the 6 Ugandan facilities, ranging from 32% (SD: 28) in 2016 to 39% (SD: 31) in 2017 (S4 Table).

Readiness loss by cascade

Along the cascades, there were notable differences in readiness loss from identification (stage 1) through monitoring-modifying therapy (stage 3). At both time-points, it varied least for neonatal resuscitation (range: 13–35) and most for respiratory distress-apnea (range: 65–74; Table 4; Figs 1–3; S1 Fig). There was mild to moderate variability in when readiness was lost along the cascade. In 2016, the majority of readiness was lost during the identification stage for all cascades except essential newborn care, which lost most readiness in the treatment stage (Table 4; Fig 4; S1 and S2 Figs). In 2017, the majority of readiness was again lost in the identification stage for respiratory distress-apnea, jaundice, and neonatal resuscitation (Table 4; Fig 3). In contrast, the infection-convulsions, essential newborn care, and poor feeding-hypothermia cascades lost most readiness in the treatment stage (Table 4; S3 and S4 Figs).

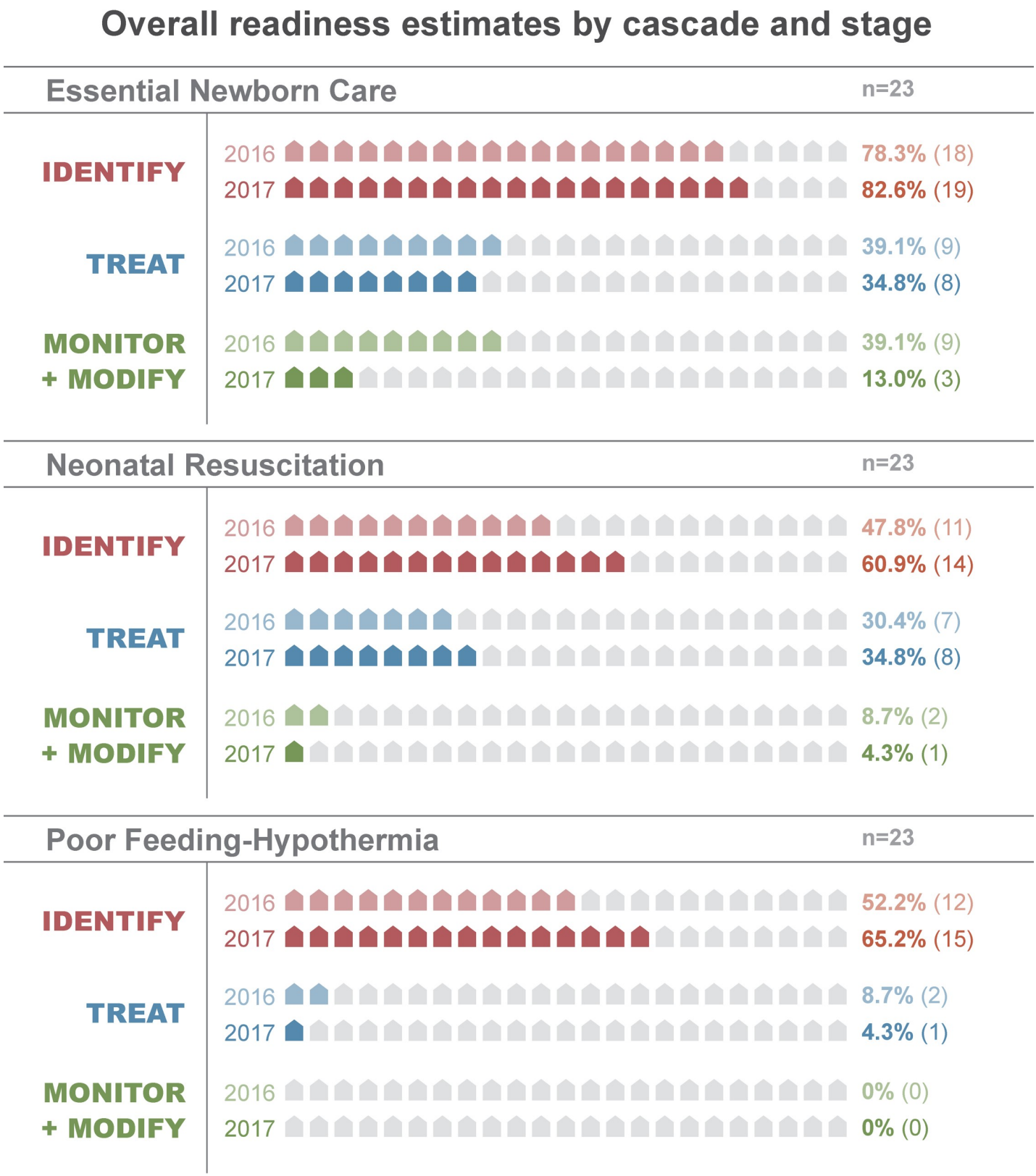

Fig 1. Comparison of overall readiness estimates by stage of care for the essential newborn care, neonatal resuscitation, and poor feeding-hypothermia clinical cascades in 2016 and 2017.

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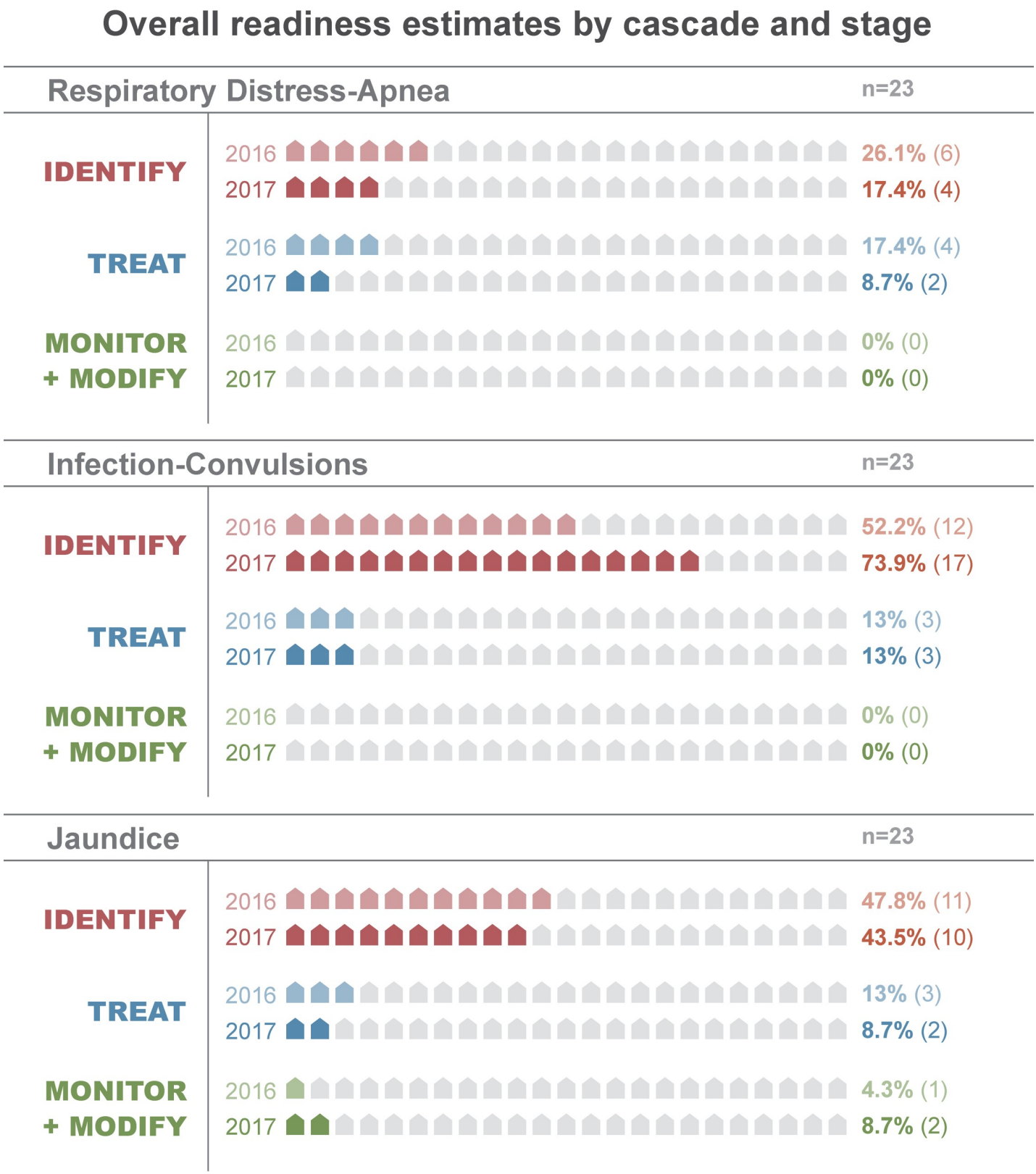

Fig 2. Comparison of overall readiness estimates by stage of care for the respiratory distress-apnea, infection-convulsions, and jaundice clinical cascades in 2016 and 2017.

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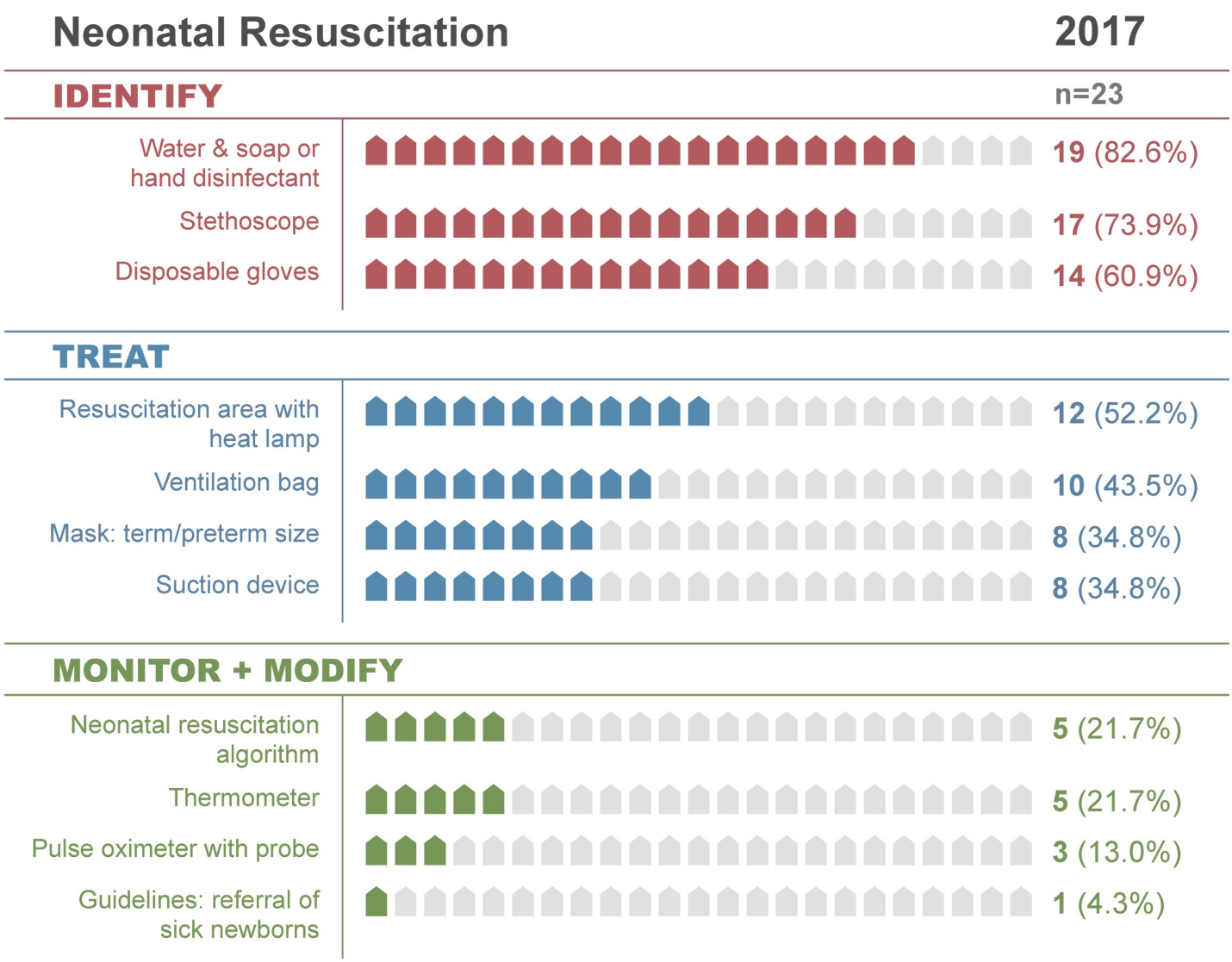

Fig 3. Neonatal resuscitation clinical cascade, 2017.

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Readiness loss by stage

Across all 6 cascades, mean readiness loss by stage ranged from 43–49% for identification, 31–40% for treatment, and 12–13% for monitoring-modifying treatment (Table 4). Across all cascades and stages, there was an increasingly consistent pattern of 30% (SD: 5) to 32% (SD: 2) overall readiness loss, with moderate variability in how loss occurred across stages (SD across stages: 20–23; Table 4).

Comparison of readiness in facilities with and without newborn special care units

Across both time-points, overall mean readiness was higher among facilities with a functional NSCU (37%) compared to those without (20%). For both groups, readiness was again lowest for respiratory distress-apnea (27% and 3%, respectively) and highest for essential newborn care (54% and 39%, respectively; Table 5). Among facilities with a NSCU, there was

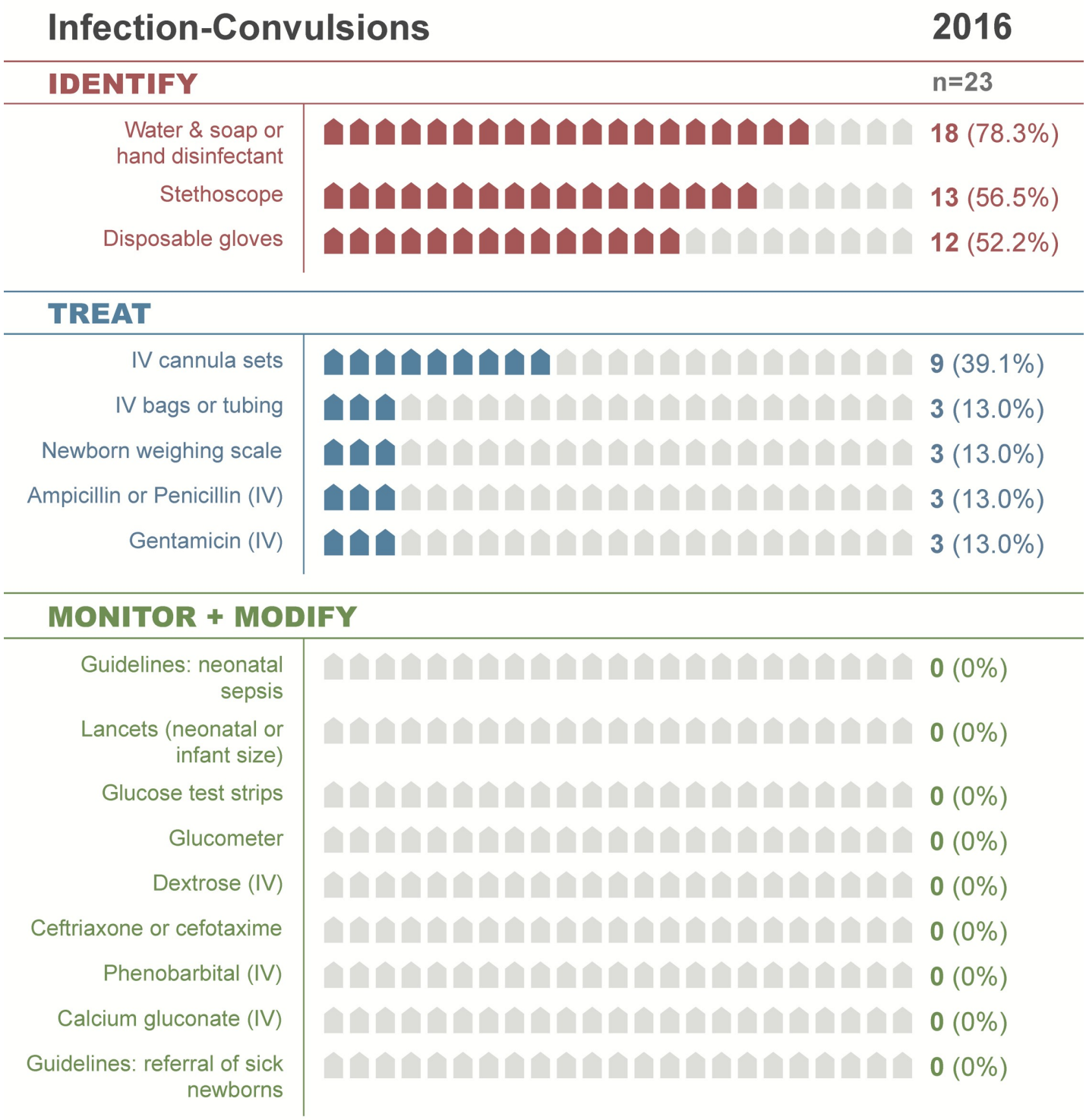

Fig 4. Infection-convulsions clinical cascade, 2016. See Table 3 for relevant footnotes.

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significantly increased identification readiness for respiratory distress-apnea (2016: 63% vs. 7%; 2017: 38% vs. 7%) and jaundice (2016: 75% vs. 33%), and treatment readiness for essential

Table 4. Readiness loss by clinical cascade and stage of care, 2016 and 2017.

	Readiness loss by stage[a]			Readiness loss by cascade		
	Identify	Treat	Monitor/Modify	Mean loss across 3 stages	SD	Range
2016						
Loss by clinical cascade						
				30[b]	20	
Essential Newborn Care	22	39	0	20	20	39
Neonatal Resuscitation	52	17	22	30	19	35
Poor Feeding-Hypothermia	48	44	9	33	21	39
Respiratory Distress-Apnea	74	9	17	33	35	65
Infection-Convulsions	48	39	13	33	18	35
Jaundice	52	35	9	32	22	44
Overall loss by stage						
Mean loss across cascade	49	31	12			
SD	17	14	8	5		
2017						
Loss by clinical cascade						
				32[b]	23	
Essential Newborn Care	17	48	22	29	16	30
Neonatal Resuscitation	39	26	31	32	7	13
Poor Feeding-Hypothermia	35	61	4	33	28	57
Respiratory Distress-Apnea	83	9	9	33	43	74
Infection-Convulsions	26	61	13	33	25	48
Jaundice	57	35	0	30	29	57
Overall loss by stage						
Mean loss across cascade	43	40	13			
SD	24	21	11	2		

[a] n = 23 facilities

[b] This figure represents overall mean readiness loss across the 3 stages for all 6 cascades.

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newborn care (2016: 75% vs. 20%), poor feeding-hypothermia (2016: 25% vs. 0%), respiratory distress-apnea (2016: 38% vs. 7%; 2017: 25% vs. 0%), and infection-convulsions (2017: 38% vs. 0%; Table 5). At the monitoring-modifying stage, a significant difference was only identified for essential newborn care (2016: 38% vs. 7%; Table 5).

Discussion

The clinical cascade model offers a novel, stepwise approach to quantitatively estimate facility readiness for neonatal care in LMICs. Cascade-derived indicators, including overall readiness, readiness loss by cascade, readiness loss by stage, and aggregate readiness loss, can be used by health administrators, policy-makers, program managers, and researchers to assess and monitor the availability of drugs, supplies, and equipment for facility-based neonatal care in such contexts. By precisely identifying the timing and location of readiness loss, by stage or clinical condition, the cascades could help guide resource allocation decisions and facilitate provision of available, evidence-based interventions to reduce neonatal morbidity and mortality [7]. Further, aggregate readiness loss may be utilized to evaluate and compare readiness for neonatal care across health systems, countries, or geographic regions [33].

In contrast to health facility inventories and signal functions widely used to evaluate EmONC capacity [16,44,45], the cascades pragmatically assess and quantify a facility's capacity

Table 5. Comparison of readiness in facilities with and without newborn special care units, 2016 and 2017.

Stage	Neonatal care cascade	2016 time-point			2017 time-point		
		NSCU present[a]	NSCU absent[b]	p-value[c]	NSCU present[a]	NSCU absent[b]	p-value[c]
Identify	Essential Newborn Care (n, %)	7 (88)	11 (73)	0.2159	7 (88)	12 (80)	0.3256
	Neonatal Resuscitation (n, %)	4 (50)	7 (47)	0.4400	6 (75)	8 (53)	0.1549
	Poor Feeding-Hypothermia (n, %)	6 (75)	6 (40)	0.0548	6 (75)	9 (60)	0.2360
	Respiratory Distress-Apnea (n, %)	5 (63)	1 (7)	0.0019	3 (38)	1 (7)	0.0318
	Infection-Convulsions (n, %)	5 (63)	7 (47)	0.2350	7 (88)	10 (67)	0.1396
	Jaundice (n, %)	6 (75)	5 (33)	0.0283	5 (63)	5 (33)	0.0892
Treat	Essential Newborn Care (n, %)	6 (75)	3 (20)	0.0050	3 (38)	5 (33)	0.4202
	Neonatal Resuscitation (n, %)	3 (38)	4 (27)	0.2960	4 (50)	4 (27)	0.1319
	Poor Feeding-Hypothermia (n, %)	2 (25)	0 (0)	0.0214	1 (13)	0 (0)	0.0807
	Respiratory Distress-Apnea (n, %)	3 (38)	1 (7)	0.0318	2 (25)	0 (0)	0.0214
	Infection-Convulsions (n, %)	2 (25)	1 (7)	0.1074	3 (38)	0 (0)	0.0055
	Jaundice (n, %)	2 (25)	1 (7)	0.1074	1 (13)	1 (7)	0.9936
Monitor-Modify	Essential Newborn Care (n, %)	3 (38)	1 (7)	0.0318	0 (0.0)	3 (20.0)	0.9125
	Neonatal Resuscitation (n, %)	1 (13)	1 (7)	0.3193	1 (13)	0 (0)	0.0807
	Poor Feeding-Hypothermia (n, %)	0 (0)	0 (0)	1.0000	0 (0)	0 (0)	1.0000
	Respiratory Distress-Apnea (n, %)	0 (0)	0 (0)	1.0000	0 (0)	0 (0)	1.0000
	Infection-Convulsions (n, %)	0 (0)	0 (0)	1.0000	0 (0)	0 (0)	1.0000
	Jaundice (n, %)	1 (13)	0 (0)	0.0807	1 (13)	1 (7)	0.9936

[a] Facilities with functional NSCU, n = 8

[b] Facilities without functional NSCU, n = 15

[c] p-values were calculated using the two-sample test of proportions, with a 95% level of confidence.

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to identify and manage six common neonatal conditions. This is accomplished by modeling the hierarchical and interdependent relationship among the resources required to identify a condition, provide initial treatment, monitor clinical response, and modify treatment if indicated [24,25]. Although additional signal functions for emergency newborn care were proposed in 2012 [18], these have not been incorporated in recent WHO guidelines [38,39]. Further, a standardized approach to evaluate readiness for basic newborn care using existing indicators is lacking [16,33].

To help address this gap, the cascade model provides an intuitive set of overall, condition-specific, and health system readiness indicators for basic and comprehensive levels of newborn care. Notably, this approach entails a negligible increase in data collection requirements compared to existing facility assessment inventories [44,45]. In addition, the neonatal cascades provide detailed information about when and where readiness loss occurs. Aggregate readiness loss can be used as a standardized indicator to quantify and compare readiness at the facility-, health system-, or national-level. This study identified a consistent pattern of 30–32% overall readiness loss across cascades and stages, which is comparable to that seen in the obstetric cascade study in Kenya [33]. The majority of readiness loss occurred in the identification stage; however, loss of treatment readiness increased in 2017, with this stage accounting for the majority of overall loss for essential newborn care, poor feeding-hypothermia, and infection-convulsions. Comparatively, the obstetric cascade study found increased variability in timing of readiness loss. For example, most loss for hypertensive emergencies occurred in the identification stage, whereas most loss for hemorrhage occurred in the monitoring-modifying stage [33].

Using the cascade model, we found that overall readiness for neonatal care was 26% among the 23 facilities at both time-points. In comparison, three studies using the EmONC signal function classification to assess a total of 431 facilities in sub-Saharan Africa and South Asia found that 0–9% and 0–23% were able to provide basic and comprehensive levels of care, respectively [19–21]. Readiness was consistently highest for essential newborn care. This may be related to the fact that resources required for comprehensive neonatal care are more expensive or difficult to maintain than those needed for essential newborn care. Additionally, previous studies evaluating facility or health system capacity have largely focused on indicators related to basic newborn care, including cleanliness, breastfeeding, cord care, tetracycline eye ointment, vitamin K, and resuscitation at birth [18–22,46–48]. Conversely, readiness was consistently lowest for respiratory distress-apnea, with only 17–26% of facilities having a pulse oximeter and other supplies required for identification. Two previous studies in Kenya similarly found that 14–18% of public referral hospitals had functional pulse oximeters for pediatric and neonatal care in 2012 [49,50]. Not surprisingly, overall readiness was higher in regional/district/county level and mission/PNFP facilities relative to sub-county and health clinic level facilities. In line with the WHO guidelines on managing possible serious bacterial infections in young infants when referral is not feasible [51], we replaced IV cannula sets with sterile syringes and needles (for IM injection) in the neonatal infection-convulsions cascade sub-analysis of health clinics. By country, overall readiness was higher in Uganda (32–39%) than in Kenya (22–23%). This is likely related to the fact that 100% of Ugandan facilities had a functional NSCU, whereas nearly 90% of Kenyan facilities did not.

Endorsed in 2014, the Every Newborn Action Plan (ENAP) is a global multi-partner initiative to prevent stillbirths and reduce neonatal mortality, with national targets of 10 or fewer deaths per 1000 livebirths by 2035 [52]. To help improve the provision of facility-based care, ENAP has recommended defining indicators for intervention packages by level of care (basic, special, or intensive care), noting that many small and sick neonates can be appropriately managed in NSCUs [3,8,23]. A Delphi study suggested that special care, including KMC, feeding support, IV fluids, oxygen, and management of infections and jaundice, could prevent 70% of deaths in preterm neonates [7]. We identified increased overall readiness among facilities with a NSCU compared to those without. Further, facilities with a NSCU had significantly increased treatment readiness for essential newborn care, poor feeding-hypothermia, respiratory distress-apnea, and infection-convulsions, relative to facilities without a NSCU. Recognizing the need to improve care for small and sick neonates, the Government of India scaled-up the establishment of NSCUs in district hospitals across the country [53–55]. A study of eight NSCUs in eight Indian states, all established within the preceding five years, demonstrated that cause-specific mortality due to sepsis and low birthweight decreased significantly over a two-year period [55].

Notably, poor-quality care is now considered to be a greater barrier to mortality reduction in LMICs than insufficient access [56]. The WHO has developed a quality of care framework for pregnant women and newborns in facilities, which highlights the overarching need for both competent human resources and essential physical resources and additionally requires evidence-based practices for routine and emergency care; actionable information systems; functional referral systems; effective communication; respect and dignity; and emotional support [57]. In recent years, increased emphasis has been placed on promotion of respectful maternity care and elimination of abuse during childbirth [58–60]. One study found that women who experience discrimination or abuse during childbirth are less likely to seek facility-based delivery care in the future [61]; such experiences may also deter postnatal care-seeking [12]. To help improve clinical outcomes for small and sick newborns, a culture of capability should be promoted in places where fatalism on the part of healthcare providers is

common [62,63]. Evidence from high- and middle-income countries has also demonstrated the value of family-centered developmental care for this vulnerable population [64–66]. A study in Colombia found that continuing education for care providers, provision of materials for positioning of neonates, and use of an informative video for parents were helpful in promoting related care practices [67].

This study has several limitations. The cascade model assesses the physical readiness of facilities to provide newborn care, but it does not assess human resource availability or health-care providers' skills. Observational data from 18 LMICs, including Kenya and Uganda, showed that providers fulfilled 45% and 64% of recommended elements of sick child and delivery care, respectively [56], highlighting the fact that provider skill assessment is also imperative. These data are from 23 facilities in two regions within two countries of East Africa, which limits generalizability to all LMIC contexts. All facility assessments were routinely conducted as part of a broader maternal and newborn health research initiative. As a result, a few variables necessary for complete modeling of the essential newborn care, infection-convulsions, and jaundice cascades were not available. Significant and unanticipated reductions in the availability of certain durable goods (e.g., resuscitation area with warmer, glucometer) were identified; however, we did not obtain data about potential reasons why these items were no longer present (or functional). Certain tracer items for basic and special levels of newborn care are poorly defined, which may slightly limit comparisons of this study with previous studies using these indicators from the literature. For example, the EmONC tracer for basic neonatal resuscitation does not specify the ventilation bag or mask size [16], and the ENAP tracer for IV fluid does not specify the type of fluid [8]. Clearly defined tracer items are imperative to standardize readiness estimates for neonatal care and promote comparability across study results and settings.

In the future, research should evaluate the neonatal cascade model in a variety of cultural, regional, and national contexts. In addition, studies comparing this novel model of neonatal care readiness with previous models may be indicated. Notably, the third stage (monitoring-modifying treatment) of each cascade includes one or more guidelines related to newborn care practices, e.g., referral of sick newborns; however, few previous studies assessing facility readiness for EmONC have utilized clinical guidelines as tracer items [33,47,68]. To assess the quality of facility-based neonatal care and compare readiness estimates using different models, inclusion of tracers for key clinical guidelines is essential. Finally, research could evaluate the ability of the cascades, employed as one component of a broader model, to predict neonatal mortality and morbidities related to the 6 conditions and explore the association between aggregate readiness loss and neonatal mortality across countries or regions.

Conclusion

In conclusion, the clinical cascade model provides a novel, stepwise approach to quantitatively assess facility readiness for neonatal care. We identified a consistent pattern of 30–32% readiness loss across cascades and stages at both time-points at 23 facilities in Kenya and Uganda. This aggregate measure could be used to monitor and compare readiness at the facility-, health system-, or national-level. Cascade-derived estimates of readiness and capacity loss may help guide strategies to improve care, prioritize resources, and promote neonatal survival in LMICs.

Supporting information

S1 Table. Frequency and proportion of facilities with durable goods for neonatal care.
(DOCX)

S2 Table. Frequency and proportion of facilities with consumable supplies for neonatal care.
(DOCX)

S3 Table. Neonatal care readiness in Kenyan and Ugandan health facilities by facility level, 2016 and 2017.
(DOCX)

S4 Table. Neonatal care readiness in Kenyan and Ugandan health facilities by country, 2016 and 2017.
(DOCX)

S1 Fig. Respiratory distress-apnea clinical cascade, 2016. See Table 3 for relevant footnotes.
(TIFF)

S2 Fig. Jaundice clinical cascade, 2016. See Table 3 for relevant footnotes.
(TIFF)

S3 Fig. Essential newborn care clinical cascade, 2017. See Table 2 for relevant footnotes.
(TIFF)

S4 Fig. Poor feeding-hypothermia clinical cascade, 2017. See Table 2 for relevant footnotes.
(TIFF)

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4. Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia (Paper B)

4.1. Scope of this chapter

Chapter 4 presents the second research paper entitled, "Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia." Existing systems to quantify neonatal illness severity and mortality risk have primarily been developed for high-income settings, often requiring complex calculations and using parameters that are infrequently available or challenging to measure accurately in resource-constrained facilities. This paper describes the development and validation of a risk score, feasible for use in LMIC settings, to predict in-hospital neonatal mortality within 24h of birth. Prompt recognition of illness and provision of evidence-based therapies are imperative to improve clinical outcomes amongst the smallest and most vulnerable newborns.

This work was published in *The Lancet Child and Adolescent Health* in February 2020 as an open access article. See Appendix A.4.1 for the copyright. The article was accompanied by a Comment in *The Lancet Child and Adolescent Health* entitled, "Neonatal risk adjustment in low-resource settings," which was authored by Shoo Lee and Qi Zhou (Annex A.4.4).

4.2. List of figures

4.3. List of tables

4.4. Citation

Medvedev MM, Brotherton H, Gai A, Tann C, Gale C, Waiswa P, Elbourne D, Lawn JE, Allen E. **Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000g or less (NMR-2000): an analysis using data from the UK and The Gambia**. *Lancet Child Adolesc Health* 2020; 4(4):299-311. doi: 10.1016/S2352-4642(20)30021-3.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	131393	**Title**	Dr
First Name(s)	Melissa Morgan		
Surname/Family Name	Medvedev		
Thesis Title	Informing the design of a trial of kangaroo mother care initiated before stabilisation amongst small and sick newborns in a sub-Saharan African context using mixed methods		
Primary Supervisor	Elizabeth Allen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	The Lancet Child and Adolescent Health as: Medvedev MM, Brotherton H, Gai A, Tann C, Gale C, Waiswa P, Elbourne D, Lawn JE, Allen E. Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia. Lancet Child Adolesc Health. 2020; 4: 299–311. doi: 10.1016/S2352-4642(20)30021-3.		
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If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not applicable		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceptualised the study with Dr Cally Tann and Profs Joy Lawn, Elizabeth Allen, and Diana Elbourne. I designed the study with Drs Cally Tann and Helen Brotherton, and Profs Joy Lawn, Elizabeth Allen, and Diana Elbourne. I developed the analytic plan with Prof Elizabeth Allen. I conducted the literature review of neonatal risk scores, with input from Prof Joy Lawn. I curated data from the UK National Neonatal Research Database, with input from Drs Christopher Gale and Cally Tann, and I provided input on the collection of validation data in The Gambia. I conducted all analyses. I wrote the first draft of the manuscript and prepared all subsequent revisions with consideration of comments from co-authors. See Annex A.1. for full details.

SECTION E

Student Signature	Melissa Medvedev
Date	3 August 2020

Supervisor Signature	Elizabeth Allen
Date	5/8/2020

Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia

Melissa M Medvedev, Helen Brotherton, Abdou Gai, Cally Tann, Christopher Gale, Peter Waiswa, Diana Elbourne, Joy E Lawn, Elizabeth Allen

Summary

Background 78% of neonatal deaths occur in sub-Saharan Africa and southern Asia, among which, more than 80% are in low birthweight babies. Existing neonatal mortality risk scores have primarily been developed for high-resource settings. The aim of this study was to develop and validate a score that is practicable for low-income and middle-income countries to predict in-hospital mortality among neonates born weighing 2000 g or less using datasets from the UK and The Gambia.

Methods This analysis used retrospective data held in the UK National Neonatal Research Database from 187 neonatal units, and data from the Edward Francis Small Teaching Hospital (EFSTH), Banjul, The Gambia. In the UK dataset, neonates were excluded if birthweight was more than 2000 g; if the neonate was admitted aged more than 6 h or following discharge; if the neonate was stillborn; if the neonate died in delivery room; or if they were moribund on admission. The Gambian dataset included all neonates weighing less than 2000 g who were admitted between May 1, 2018, and Sept 30, 2019, who were screened for but not enrolled in the Early Kangaroo Mother Care Trial. 18 studies were reviewed to generate a list of 84 potential parameters. We derived a model to score in-hospital neonatal mortality risk using data from 55 029 admissions to a random sample of neonatal units in England and Wales from Jan 1, 2010, to Dec 31, 2016. All candidate variables were included in a complete multivariable model, which was progressively simplified using reverse stepwise selection. We validated the new score (NMR-2000) on 40 329 admissions to the remaining units between the same dates and 14 818 admissions to all units from Jan 1, to Dec 31, 2017. We also validated the score on 550 neonates admitted to the EFSTH in The Gambia.

Findings 18 candidate variables were selected for inclusion in the modelling process. The final model included three parameters: birthweight, admission oxygen saturation, and highest level of respiratory support within 24 h of birth. NMR-2000 had very good discrimination and goodness-of-fit across the UK samples, with a c-index of 0·8859–0·8930 and a Brier score of 0·0232–0·0271. Among Gambian neonates, the model had a c-index of 0·8170 and a Brier score of 0·1688. Predictive ability of the simplified integer score was similar to the model using regression coefficients, with c-indices of 0·8903 in the UK full validation sample and 0·8082 in the Gambian validation sample.

Interpretation NMR-2000 is a validated mortality risk score for hospitalised neonates weighing 2000 g or less in settings where pulse oximetry is available. The score is accurate and simplified for bedside use. NMR-2000 requires further validation using a larger dataset from low-income and middle-income countries but has the potential to improve individual and population-level neonatal care resource allocation.

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Introduction

An estimated 2·5 million neonatal deaths occurred in 2018, accounting for 47% of deaths among children younger than 5 years.[1] The burden of neonatal mortality is unequally distributed, with nearly 80% of these deaths occurring in sub-Saharan Africa and southern Asia.[1] Between 2000 and 2015, neonatal mortality declined more slowly than mortality among children aged 1–59 months. This disparity was particularly notable in sub-Saharan Africa, where the annual mortality reduction for newborn babies was less than half of that for 1–59 month-olds.[2] Slow progress in this region might be related to high incidences of preterm birth (<37 completed weeks of gestation) and low birthweight (≤2000 g),[3,4] poor access to care for neonates,[5,6] and health system capacity issues, including

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Research in context

Evidence before this study

2·5 million neonatal deaths occur each year, among which 78% are in sub-Saharan Africa and southern Asia. More than 80% of these deaths occur in babies with a low birthweight who are small because they are preterm, small for their gestational age, or both. There has been slow progress in reducing neonatal mortality, which accounts for nearly half of deaths in children younger than 5 years, highlighting the need for scale-up of effective interventions for neonates who are at risk. We searched PubMed for studies published between Jan 1, 1992, and July 31, 2019, with the search terms "infant, newborn", and "infant mortality", or "infant, newborn, diseases, and mortality", or "infant, premature, diseases, and mortality", or "hospital mortality", and "severity of illness index", or "risk assessment", or "predictive value of tests", or "outcome assessment". Multiple risk scores for neonatal mortality, illness severity, and clinical instability have been developed for intensive care settings. Most of these risk scores are not feasible for low-income and middle-income countries, because they rely on laboratory-derived and therapy-derived parameters that are frequently unavailable, or on clinical observations that are not reliably measurable. A need remains for a highly predictive tool, feasible for use in resource-constrained settings, to help providers objectively assess mortality risk in the most vulnerable babies.

Added value of this study

Using population-wide data from 110 176 neonates admitted to 187 hospitals across England and Wales, this study has derived and validated a mortality risk score for neonates weighing 2000 g or less (NMR-2000). To our knowledge, this is the largest dataset used to develop and validate a neonatal mortality risk score. NMR-2000 uses data on three parameters: birthweight, oxygen saturation (peripheral capillary oxygen) at admission, and highest level of respiratory support at any point within 24 h of birth. The model had very good discrimination and goodness-of-fit across the development and UK validation samples, with a c-index of 0·8859–0·8930 and a Brier score of 0·0232–0·0271. The simplified integer score, which can be measured and calculated at the bedside, showed predictive ability similar to the model using regression coefficients. In the Gambian dataset, which included 550 neonates at one hospital, the model had good discrimination and overall goodness-of-fit, with a c-index of 0·8170 and a Brier score of 0·1688. The simplified integer score showed similar performance, with a c-index of 0·8082. Complete data for scoring were available for 83% of neonates. These findings indicate that the NMR-2000 is valid for use in health facilities where pulse oximetry is available and underscore the fact that implementation in low-income and middle-income countries would require sensitisation regarding documentation of the three parameters used in the model.

Implications of all the available evidence

To reduce neonatal mortality worldwide, there is an urgent need to scale-up evidence-based interventions targeting the major causes of death. Our risk score could expedite recognition of severe illness and enable targeted delivery of care to small and vulnerable neonates, increasing effectiveness and efficiency of facility-based neonatal care in low-income and middle-income countries. Further research is required to validate NMR-2000 in low-resource settings using a larger sample, and to evaluate its usefulness for clinical decision making. The score has the potential to inform resource use, including nursing workload.

shortages of skilled providers, essential supplies, and basic equipment.[6–8]

More than 80% of neonatal deaths in sub-Saharan Africa and southern Asia occur in babies with a low birthweight.[9] Low birthweight can result from being preterm, being small for their gestational age, or both. Mortality is twice as high in full-term neonates who are small for their gestational age than in full-term neonates who are of average size, and 15 times higher in preterm neonates who are small for their gestational age than in babies with either characteristic alone.[10] The lower the birthweight and gestational age, the higher the mortality risk.[9] Around 86% of neonates born at fewer than 28 weeks' gestation, and 41% of those born at 28–31 weeks, will die without access to intensive care;[11] more than 75% of neonates in sub-Saharan Africa and southern Asia have no access to such care.[7] Estimates suggest that neonatal special care,[5,7] including resuscitation, kangaroo mother care, feeding support or intravenous fluids, and management of respiratory distress, infections, and jaundice, could prevent 70% of preterm deaths and decrease prematurity-related causes of neonatal mortality by 58%.[12]

See Online for appendix

Various systems for scoring illness severity and mortality risk in neonates have been developed, primarily for high-income settings (appendix p 6). Therapy-based approaches, such as the Neonatal Therapeutic Intervention Scoring System (NTISS),[13] categorise illness severity by the quantity and type of therapies administered. By contrast, the Score for Neonatal Acute Physiology (SNAP),[14,15] the Transport Risk Index of Physiologic Stability (TRIPS),[16] and other physiology-based approaches use objective, measurable parameters that vary with illness severity, such as blood pressure. Related models, such as the Clinical Risk Index for Babies (CRIB),[17,18] combine physiological parameters with perinatal factors, such as birthweight, to provide an overall mortality risk score. SNAP and CRIB are the most widely used systems and have been extensively validated.[19]

Notably, none of the aforementioned systems are practicable for routine use in low-income and middle-income countries (LMICs), because these systems rely on laboratory-derived and therapy-derived measures that are often not available, or on clinical observations that are not reliably measurable in these settings.[20–22] The simplified age-weight-sex (SAWS) score is the only validated neonatal mortality score designed for low-resource settings. Among a derivation cohort of 428 neonates weighing 1500 g or less in Bangladesh and Egypt, the SAWS was reported to have moderate discrimination for in-hospital mortality.[22] To improve the quality of facility-based neonatal care in LMICs, a highly predictive tool, which is feasible for routine use, is needed to help providers objectively assess mortality risk in small babies.

This study has two parts: (1) model development using data from the UK, and (2) model validation using data from the UK and The Gambia. The objectives were to evaluate existing neonatal illness severity and mortality risk scores to select candidate variables for use in the new model; develop and validate a score feasible for use in LMICs to predict in-hospital neonatal mortality risk among neonates weighing 2000 g or less within 24 h of birth; and compare the performance of the novel score (NMR-2000) with that of an existing score (CRIB-II).

Methods

Study design and participants

This retrospective study used data held in the UK National Neonatal Research Database (NNRD) from 187 neonatal units to develop a model for scoring in-hospital neonatal mortality risk in LMICs. The NNRD holds de-identified patient-level data, recorded by health-care providers as part of routine care, from admissions to National Health Service neonatal units in England starting from 2008, and in Wales and Scotland starting from 2012. This study included neonates admitted to units in England and Wales between Jan 1, 2010, and Dec 31, 2017 (appendix p 1). The following exclusion criteria were also applied: birthweight more than 2000 g; being admitted at older than 6 h or following discharge home; neonates who were stillborn; neonates who died in the delivery room; neonates who were moribund (received only comfort care before death; appendix p 1).

As well as data from the NNRD, we used data on neonates in The Gambia. West and central Africa have the highest neonatal mortality worldwide (31 in 1000 livebirths).[1] In The Gambia in 2018, the neonatal mortality (26 in 1000 livebirths) ranked ninth among the 16 countries of west Africa.[1] An estimated 12% of Gambian neonates are born preterm.[3] Edward Francis Small Teaching Hospital (EFSTH) in Banjul is the national referral hospital where the neonatal unit admits around 1400 neonates annually. From 2010 to 2013, case-fatality was 35% overall and prematurity-related complications were the leading cause of death.[23]

The Gambian cohort included all neonates weighing less than 2000 g who were admitted to EFSTH between May 1, 2018, and Sept 30, 2019, who were screened for but not enrolled in the Early KMC (eKMC) trial (NCT03555981). Some routine data, including mode of delivery and treatments administered, were collected from medical charts by trained study personnel. Other data collected as part of the screening process were exported from the trial database, including birthweight, sex, birth plurality, referral status, and peripheral capillary oxygen saturation (SpO_2; appendix p 1).

Model development and validation using the UK dataset was approved by the North West–Preston Research Ethics Committee (17/NW/0709), the UK Health Research Authority, and the London School of Hygiene and Tropical Medicine (LSHTM; reference number 14594). Letters were sent to the UK Neonatal Collaborative Lead of all units contributing data to the NNRD, providing information about the study and giving each an opportunity to opt out. Model validation using the Gambian dataset was approved by research ethics committees of the Gambian Government and Medical Research Council Unit The Gambia at the LSHTM (reference number 1643) and LSHTM (reference number 16189). Consent was not obtained, as this was a retrospective study using de-identified data.

Selection of candidate variables

To select the candidate variables for the model, 18 studies describing existing systems for assessing neonatal mortality risk and illness severity were reviewed to generate a list of potential parameters (appendix p 6). Parameters that are typically unavailable, infrequently obtained, or unreliably measured in low-resource settings were excluded (appendix p 1). Remaining parameters were evaluated using the following exclusion criteria: low prevalence in the NNRD (<0·1%); high proportion of missing data in the development dataset (≥20%); not predictive of mortality in neonates who are preterm or have a low birthweight; low prevalence within the first 24 h of life; little evidence to support validity; and concept better represented by an alternative variable (appendix pp 7–9).

Model development

To create the model, we used a development sample of neonates admitted to a random sample of neonatal units in England and Wales from Jan 1, 2010, to Dec 31, 2016. Logistic regression models were derived to model in-hospital mortality risk. Robust standard errors allowed for clustering within units. All candidate variables were included in a complete multivariable model, which was progressively simplified using reverse stepwise selection, with the least statistically significant variable removed at each step. Discrimination was assessed with the c-index, equivalent to the area under the receiver operating characteristic (ROC) curve. A value of 0·5 indicates no predictive ability, 0·8 is considered good, and 1 is perfect.[21]

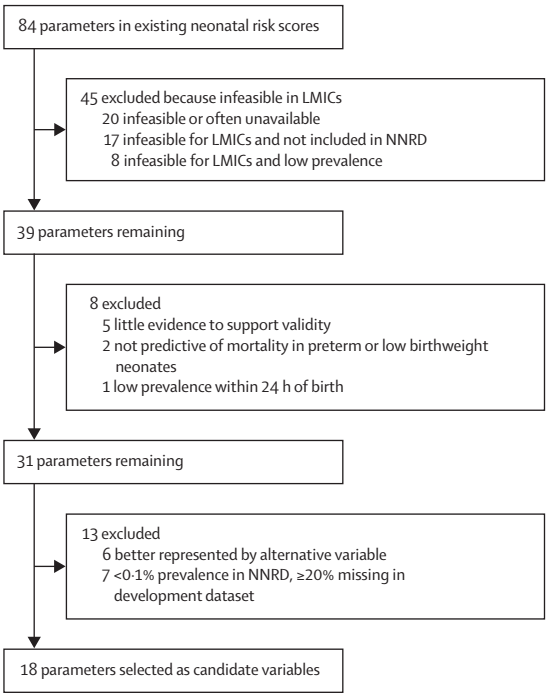

Figure 1: **Flow chart showing filtration of parameters from existing risk scores to select candidate variables**
LMICs=low-income and middle-income countries. NNRD=National Neonatal Research Database.

Overall goodness-of-fit was assessed with the Brier score and calibration using plots of observed versus predicted risk (appendix p 2). Multiple imputation with chained equations was used to assess the effect of missing data (appendix p 2). The logistic regression model was executed across the imputed datasets, and the resulting β coefficients and c-index were compared with original estimates. A sensitivity analysis excluding neonates whose admission age was unknown (anonymised data derived from calculated difference between birth time and admission time) was done to reassess model performance, because admission at more than 6 h of age was an exclusion criterion. Performance was additionally reassessed following exclusion of neonates who were transferred for any reason because outcome data were not available for these babies. Performance for predicting mortality within 24 h of birth was evaluated in a secondary analysis, because 36% of neonatal deaths occur within this timeframe.[24]

Score development

To develop the score, we assigned the parameters in the final model points proportional to their β regression coefficient values. Whole numbers were used to generate an easily calculable score. We arbitrarily defined low-risk, medium-risk, and high-risk groups (appendix pp 2–3). To assess the calibration of the score to the model using regression coefficients, observed risks in groups and population deciles of scores were derived and compared with mean predicted risks in each group or population decile. We assessed overall predictive ability of the score using the c-index.

Panel: **Candidate variables evaluated in the modelling process**

Clinical signs and observations
- Heart rate at admission
- Respiratory rate at admission
- Temperature at admission
- Oxygen saturation (SpO_2) at admission
- Convulsions within 24 h of birth, defined as the presence of any clinical or electrographic seizures
- Clinically relevant increase in apnoea or brachycardia episodes, oxygen requirement, ventilatory support, or respiratory rate within 24 h of birth*

Therapy-based variables
- Bag-mask resuscitation at delivery
- Intravenous fluids within 24 h of birth
- Antibiotic therapy within 24 h of birth
- Oxygen therapy within 24 h of birth†
- Highest level of respiratory support administered at any point within 24 h of birth‡
- Caffeine (or aminophylline) within 24 h of birth
- Anticonvulsant therapy within 24 h of birth

Perinatal factors
- Sex
- Birthweight
- Gestational age
- Small for gestational age§
- Presence of visually recognisable anomaly at birth¶

SpO_2=peripheral capillary oxygen saturation. FiO_2=fraction of inspired oxygen. *Defined as an increase that was clinically significant enough to necessitate obtaining a culture to evaluate for suspected sepsis, at any point within 24 h of birth. †Defined as delivery of supplemental oxygen (FiO_2 >0·21) via any method at any point within 24 h of birth. ‡Not including initial resuscitation at birth; level 1 defined as nasal cannula or headbox; level 2 defined as continuous positive airway pressure, bilevel or synchronised intermittent positive airway pressure, or invasive ventilation with an endotracheal tube or tracheostomy. §Defined as birthweight less than the 5th percentile for gestational age, using UK-WHO standards.[26] ¶Defined as the presence of one or more of the following: cleft lip or palate; microcephaly; trisomy 13, trisomy 18, or trisomy 21; spina bifida, myelomeningocele, or meningocele; encephalocele; anencephaly; holoprosencephaly or prosencephaly; ambiguous genitalia; hypospadias; absent anus; gastroschisis; exomphalos or omphalocele; achondroplasia; Noonan syndrome.

Model validation

We then evaluated both the internal and external validity of the model. Internal validity is the reproducibility of a prediction model for the underlying population from which the data originated.[25] Bootstrap resampling with 1000 samples from within the development sample was used to internally validate the model, estimating optimism-adjusted measures of discrimination and goodness-of-fit in each bootstrap sample (appendix p 3). Performance of the refitted model in each bootstrap sample was compared with that of the refitted model in the original development

	Development sample (55 029 eligible neonates; 112 neonatal units)	External validation samples		
		Random (40 329 eligible neonates; 75 neonatal units)	Temporal (14 818 eligible neonates; 167 neonatal units)	Full (55 147 eligible neonates; 173 neonatal units)
Birthweight				
Extremely low birthweight (<1000 g)	7518 (13·7%)	5705 (14·2%)	2238 (15·1%)	7943 (14·4%)
Very low birthweight (1000–1499 g)	15 475 (28·1%)	11 290 (28·0%)	4198 (28·3%)	15 488 (28·1%)
Low birthweight (1500–2000 g)	32 021 (58·2%)	23 324 (57·9%)	8381 (56·6%)	31 705 (57·5%)
Birthweight data missing*	15 (0·03%)	10 (0·02%)	1 (<0·01%)	11 (0·02%)
Gestational age (weeks)				
Extremely preterm (<28)	6969 (12·7%)	5203 (12·9%)	1990 (13·4%)	7193 (13·1%)
Very preterm (28–31)	17 810 (32·4%)	13 108 (32·5%)	4963 (33·5%)	18 071 (32·8%)
Moderate-late preterm (32–36)	28 241 (51·3%)	20 604 (51·1%)	7470 (50·4%)	28 074 (50·9%)
Full term (37–42)	1996 (3·6%)	1408 (3·5%)	393 (2·7%)	1801 (3·3%)
Gestational age data missing	13 (0·02%)	6 (0·02%)	2 (0·01%)	8 (0·01%)
Size at gestation				
Small for gestational age	11 039 (20·1%)	7965 (19·8%)	2816 (19·0%)	10 781 (19·6%)
Size at gestation data missing	16 (0·03%)	10 (0·03%)	2 (0·01%)	12 (0·02%)
Sex				
Male	27 361 (49·9%)	20 307 (50·4%)	7490 (50·6%)	27 797 (50·4%)
Sex data missing	72 (0·1%)	30 (0·07%)	18 (0·1%)	48 (0·09%)
Mode of delivery				
Spontaneous vaginal	16 361 (32·3%)	12 404 (32·6%)	4227 (30·5%)	16 631 (32·0%)
Caesarean section	32 473 (64·1%)	24 404 (64·0%)	9148 (66·1%)	33 552 (64·6%)
Assisted vaginal	1820 (3·6%)	1284 (3·4%)	463 (3·3%)	1747 (3·4%)
Mode of delivery data missing	4375 (8·0%)	2237 (5·5%)	980 (6·6%)	3217 (5·8%)
Multiple birth				
Yes	16 933 (30·8%)	12 056 (29·9%)	4442 (30·0%)	16 498 (29·9%)
Multiple birth data missing	22 (0·04%)	8 (0·02%)	2 (0·01%)	10 (0·02%)
Location of birth				
Inborn†	53 954 (98·1%)	39 481 (98·0%)	14 476 (97·9%)	53 957 (98·0%)
Location of birth data missing	7 (0·01%)	36 (0·09%)	33 (0·2%)	69 (0·1%)
Location of care				
Neonatal intensive care unit‡	24 018 (43·7%)	22 362 (55·3%)	7506 (50·7%)	29 840 (54·1%)
Local neonatal unit§	26 276 (47·8%)	13 541 (33·5%)	6054 (40·9%)	19 541 (35·4%)
Special care baby unit¶	4730 (8·6%)	4538 (11·2%)	1258 (8·5%)	5766 (10·5%)
Location of care data missing	5 (0·01%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Age at admission (min)				
Median (IQR)	21 (13–33)	21 (13–34)	23 (15–35)	22 (14–34)
Age at admission data missing	5 (0·01%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Disposition				
Died before discharge	1653 (3·0%)	1306 (3·2%)	395 (2·8%)	1701 (3·1%)
Extremely low birthweight (<1000 g)	1159 (15·4%)	929 (16·3%)	280 (12·5%)	1209 (15·2%)
Very low birthweight (1000–1499 g)	295 (1·9%)	228 (2·0%)	67 (1·6%)	295 (1·9%)
Low birthweight (1500–2000 g)	199 (0·6%)	149 (0·6%)	48 (0·6%)	197 (0·6%)
Died within 24 h of birth	207 (0·4%)	194 (0·5%)	50 (0·3%)	244 (0·4%)
Transferred to another care unit‖	12 793 (23·3%)	10 119 (25·1%)	4268 (30·3%)	14387 (26·5%)
Disposition data missing	73 (0·1%)	32 (0·1%)	726 (4·9%)	758 (1·4%)
Age at discharge (days)				
Median (IQR)	22 (12–38)	21 (11–36)	19 (10–34)	20 (11–36)
Age at discharge data missing	21 (0·04%)	13 (0·03%)	740 (5·0%)	754 (1·4%)

(Table 1 continues on next page)

	Development sample (55 029 eligible neonates; 112 neonatal units)	External validation samples		
		Random (40 329 eligible neonates; 75 neonatal units)	Temporal (14 818 eligible neonates; 167 neonatal units)	Full (55 147 eligible neonates; 173 neonatal units)
(Continued from previous page)				
Variables collected at time of birth				
Bag-mask resuscitation at delivery	24 302 (44·2%)	18 297 (45·4%)	6131 (41·4%)	24 428 (44·3%)
Visually recognisable anomaly	1299 (2·4%)	1151 (2·9%)	309 (2·1%)	1460 (2·7%)
Variables collected at time of admission				
Heart rate (beats per min), mean (SD)	153·4 (18·4)	153·8 (18·7)	154·5 (18·6)	154·0 (18·6)
Heart rate data missing	7197 (13·1%)	3557 (8·8%)	1234 (8·3%)	4791 (8·7%)
Respiratory rate (breaths per min), mean (SD)	53·3 (29·8)	52·4 (12·9)	52·5 (13·2)	52·4 (13·0)
Respiratory rate data missing	9535 (17·3%)	5377 (13·3%)	2008 (13·6%)	7385 (13·4%)
Temperature (°C), mean (SD)	36·6 (0·7)	36·6 (0·7)	36·7 (0·8)	36·6 (0·7)
Temperature data missing	589 (1·1%)	371 (0·9%)	166 (1·1%)	537 (1·0%)
SpO_2 (%), median (IQR)	96 (93–98)	96 (92–99)	96 (93–99)	96 (93–99)
SpO_2 data missing	7787 (14·2%)	4213 (10·4%)	1392 (9·4%)	5605 (10·2%)
Variables collected within 24 h of birth				
Increased apnoea or bradycardia, oxygen, ventilatory support, or respiratory rate	3005 (5·5%)	2458 (6·1%)	903 (6·1%)	3361 (6·1%)
Convulsions	134 (0·3%)	81 (0·2%)	24 (0·2%)	105 (0·2%)
Convulsions data missing	579 (1·1%)	456 (1·1%)	297 (2·0%)	753 (1·4%)
Oxygen therapy	13 998 (25·4%)	10 989 (27·3%)	5178 (34·9%)	16 167 (29·3%)
Highest level of respiratory support				
Nasal cannula or headbox	3722 (7·0%)	2758 (7·0%)	2035 (13·9%)	4793 (8·9%)
CPAP, BiPAP or SiPAP, or invasive ventilation	23 374 (43·8%)	16 676 (42·6%)	6427 (43·8%)	23 103 (42·9%)
Respiratory support data missing	1658 (3·0%)	1161 (2·9%)	150 (1·0%)	1311 (2·4%)
Other interventions				
Intravenous fluids	41 506 (75·4%)	30 468 (75·6%)	11 697 (78·9%)	42 165 (76·5%)
Antibiotic therapy	39 774 (72·3%)	29 877 (74·1%)	11 152 (75·3%)	41 029 (74·4%)
Caffeine citrate	14 276 (25·9%)	10 862 (26·9%)	5438 (36·7%)	16 300 (29·6%)
Anticonvulsant therapy	162 (0·3%)	150 (0·4%)	45 (0·3%)	195 (0·4%)

Data are complete except where missing data are detailed; missing data are the total number of neonates for whom data are not available. Data are n (%) except where otherwise indicated. See panel for definitions of variables. CPAP=continuous positive airway pressure. BiPAP=bilevel positive airway pressure. SiPAP=synchronised intermittent positive airway pressure. SpO_2=peripheral capillary oxygen saturation. *For neonates whose birthweight was missing, admission weight was used to determine eligibility. †Inborn is defined as birth at the hospital of neonatal unit admission. ‡Intensive care units provide care for the sickest neonates who require constant supervision and monitoring, including those born at fewer than 27 weeks' gestational age: care typically includes mechanical ventilation; surgery services offered in some units; care is analogous to American Academy of Paediatrics levels 3 and 4.[27] §Local neonatal units provide full care for the majority of babies more than 27 weeks' gestational age, including short periods of intensive care; therapies provided include continuous monitoring, CPAP, and parenteral nutrition. ¶Special care units provide care for all other babies who could not reasonably be cared for at home; therapies provided include cardiorespiratory monitoring, nasogastric feeding, supplemental oxygen, and phototherapy. ||Transfer to another care unit from the initial unit of neonatal admission.

Table 1: **Characteristics of the participants in the data samples from the UK National Neonatal Research Database**

sample; estimates of optimism were averaged and subtracted to provide optimism-adjusted measures.

External validity is the generalisability of a model's performance to related populations.[25] The model was evaluated in three external validation samples: the random sample, which included neonates admitted to the units withheld from the development sample; the temporal sample, which included neonates admitted to units in England and Wales from Jan 1, to Dec 31, 2017; and the Gambian sample, which included neonates admitted to EFSTH between May 1, 2018, and Sept 30, 2019. Each sample was used to assess distinctive features of model performance. The random sample tested performance in different care settings in the UK within the same timeframe, whereas the temporal sample tested performance during a later timeframe. The Gambian sample was used to test performance in a LMIC care setting. We assessed model performance in each validation sample separately and in the UK full (combined random and temporal samples) validation sample. Discrimination was evaluated using the c-index, and goodness-of-fit was evaluated using the Brier score. Calibration was assessed by plotting observed versus predicted risk. We assessed the overall predictive ability of the risk score using the c-index.

In the Gambian sample, we redefined low-risk, medium-risk, and high-risk groups to account for increased case fatality in this sample compared with the UK samples (appendix p 3). Observed risks in groups and population deciles of scores were derived and compared with mean predicted risks in each group or population decile of the Gambian sample.

Comparison with the CRIB II score

The NNRD did not include all the variables required for calculation of CRIB, SNAP, SNAP-II, SNAPPE-II, TRIPS, or TRIPS-II scores (appendix pp 7–9); therefore, CRIB-II was selected for comparison with NMR-2000 (appendix p 3). Because CRIB-II has only been validated for use in neonates born up to 32 weeks' gestation,[18] we compared c-indices for CRIB-II and NMR-2000 among neonates born at 32 weeks' gestation or earlier in the full validation sample. All analyses were completed using Stata (version 15).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

For the selection of candidate variables, 18 studies were reviewed to generate a list of 84 potential parameters. 45 (53·6%) of 84 parameters were considered infeasible for LMICs and were excluded, among which, 25 (55·5%) also had a low prevalence or were not included in the NNRD (figure 1). Eight (9·5%) of 84 parameters were excluded because the evidence was scarce, because the parameters had poor predictive ability in preterm neonates or neonates with low birthweight, or because the parameter had a low prevalence within 24 h of birth. 18 candidate variables were selected for inclusion in the modelling process (panel).

110 176 neonates were included in the UK development and validation samples. Characteristics of the samples and participants are shown in table 1. More than half (56·6–58·2%) of the neonates had low birthweight (1500–2000 g), 28·0–28·3% had very low birthweight (1000–1499 g), and 13·7–15·1% had extremely low birthweight (<1000 g). Around half (50·4–51·3%) of the neonates were moderate-late preterm (32–36 weeks) and one-third (32·4–33·5%) were very preterm (28–31 weeks). Overall case-fatality was similar across samples (2·8–3·2%). Case-fatality of neonates with extremely low birthweight in the temporal sample (280 [12·5%] of 2238) was lower than in the other samples. No neonatal units declined to contribute data.

Characteristics of the 550 neonates in the Gambian validation sample are shown in table 2. Among the 550 neonates, 298 (54·2%) had a low birthweight, 189 (34·4%) had a very low birthweight, and 63 (11·5%) had an extremely low birthweight. 142 (25·8%) of 550 neonates were multiple births (eg, twins), 299 (54·5%) of 549 were inborn, and 215 (41·4%) of 520 died.

	Neonates with available data*	Neonates with characteristic
Birthweight†	550 (100%)	..
Extremely low birthweight (<1000 g)	..	63 (11·5%)
Very low birthweight (1000–1499 g)	..	189 (34·4%)
Low birthweight (1500 to 2000 g)	..	298 (54·2%)
Sex†	549 (99·8%)	..
Male sex	..	261 (47·5%)
Mode of delivery†	488 (88·7%)	..
Spontaneous vaginal	..	342 (70·1%)
Caesarean section	..	140 (28·7%)
Assisted vaginal	..	6 (1·2%)
Multiple birth†	550 (100%)	..
Yes	..	142 (25·8%)
Inborn‡†	549 (99·8%)	..
Yes	..	299 (54·5%)
Died before discharge†	520 (94·5%)	..
Total	..	215 (41·4%)
Extremely low birthweight (<1000 g)	..	55/61 (90·2%)§
Very low birthweight (1000–1499 g)	..	93/179 (52·0%)§
Low birthweight (1500–2000 g)	..	67/280 (23·9%)§
Oxygen saturation at admission	513 (93·3%)	..
SpO_2 (%) at admission¶	..	92% (83–96)
Highest level of respiratory support within 24 h of birth†	494 (89·8%)	..
Nasal cannula	..	294 (59·5%)
CPAP ventilation	..	53 (10·7%)

Data are n (%), n/N (%), median (IQR). See panel for definition of variables. CPAP=continuous positive airway pressure. SpO_2=peripheral capillary oxygen saturation. *Out of the total 550 neonates. †Information is included on routine admission forms. ‡Defined as birth at the study hospital. §Proportion of babies in each birthweight category who died (outcome data were not available for 5·5% of babies). ¶Information collected for the trial (eKMC trial).

Table 2: **Characteristics of participants in the Gambian validation sample**

The full model (18 variables) had a c-index of 0·9223 in the development sample (n=41 514). After stepwise elimination, the final model included three variables (table 3), with a c-index of 0·8883 and a Brier score of 0·0232 (table 4). Complete data on all three variables were available for 46 108 (83·8%) of 55 029 neonates in the development sample. After imputation of missing values for predictor variables (n=54 956), the resulting β coefficients were nearly identical to original estimates (appendix p 9) and model performance was unchanged (c-index 0·8894; appendix p 2). Admission age was uncertain for 5 (0·01%) of 55 029 neonates; in a sensitivity analysis excluding these neonates, there was no change in performance (c-index 0·8886, Brier score 0·0232).

	β coefficient	95% confidence interval*	Integer-points†	c-index
Birthweight (g)	–0·0032	–0·0035 to –0·0029	Birthweight/100	0·8540
Highest respiratory support within first 24 h	..	..	..	0·7529
Nasal cannula or headbox	0·3167	–0·1055 to 0·7389‡	–1	..
CPAP, BiPAP or SiPAP, or invasive ventilation	1·6214	1·2682 to 1·9746‡	–5	..
SpO_2 at admission	–0·0390	–0·0455 to –0·0326	..	0·6712
<80% (reference level)	..	..	0§	..
80–89%	–0·7694	–1·0093 to –0·5294	2§	..
90–100%	–1·3697	–1·6019 to –1·1376	4§	..
Constant	2·6142¶	1·7655 to 3·4629	..	..

n=46 108. CPAP=continuous positive airway pressure. BiPAP=bilevel positive airway pressure. SiPAP=synchronised intermittent positive airway pressure. SpO_2=peripheral capillary oxygen saturation. *p<0·0001 for estimates for all variables. †Calculated by multiplying the β coefficient by a constant (–3·13) and rounding to the nearest integer. The reciprocal of the coefficient for birthweight divided by 100 ([1/–0·0032]/100=–3·13) was used as the constant to retain the exact birthweight (per 100 g) in the score. ‡p<0·0001 for overall effect of level of respiratory support. §The continuous SpO_2 parameter was categorised into clinically meaningful categorical variables; the β coefficients of these variables were multiplied by the constant to obtain integer-points; the reference level (<80%) was assigned zero points. ¶Reflects β coefficient for constant in model including SpO_2 as a continuous variable.

Table 3: **Derivation logistic model for the NMR-2000 score**

	Development sample (n=46 108)		External validation samples			
	Original	Optimism-adjusted*	Random (n=35 193)	Temporal (n=12 653)	Full (n=47 846)	Gambian (n=457)
Brier score	0·0232	0·0233	0·0271	0·0240	0·0263	0·1688
c-index	0·8883	0·8882	0·8930	0·8859	0·8912	0·8170

*Because optimism-adjusted estimates of the c-index and Brier score were nearly identical to the original estimates, no adjustments were made to the model coefficients.

Table 4: **Model performance in the development and validation samples**

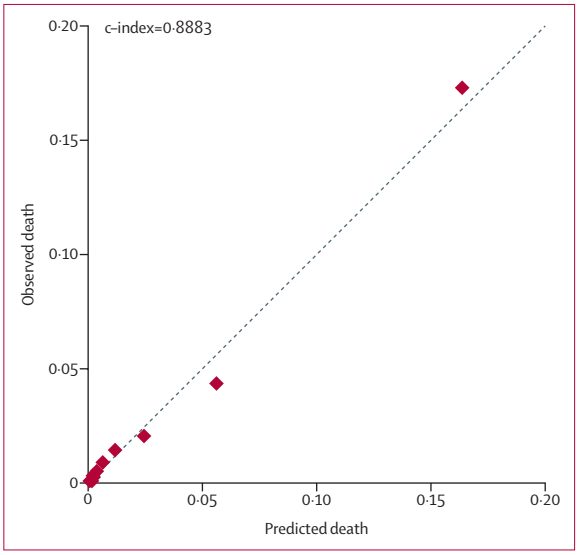

Figure 2: **Predicted versus observed death for population deciles by predicted risk in the development sample**
n=46 108. Graph created using pmcalplot.

12 793 (23·3%) of 54 956 neonates were transferred from the unit of admission to another care unit; an analysis excluding these neonates showed improved performance (c-index 0·9150, Brier score 0·0255; appendix p 2). Predictive accuracy for mortality within 24 h (c-index 0·8858, Brier score 0·0037) was nearly identical to that for in-hospital mortality. Because availability of SpO_2 monitoring is variable in LMIC settings, we tested a related variable (clinically relevant increase in apnoea or bradycardia, oxygen requirement, ventilatory support, or respiratory rate); however, this variable was not associated with in-hospital mortality (c-index 0·5061). A plot of observed versus predicted mortality risk in the development sample is shown in figure 2.

Birthweight was the most predictive variable in the model (c-index 0·8540). The reciprocal of the coefficient for birthweight divided by 100 ([1/–0·0032]/100=–3·13) was used as the constant to enable retention of exact birthweights in score calculation (table 3),[28] thereby improving predictive ability. The score range for low risk was set at 16 or more, for medium risk at 6–15, and for high risk at 5 or fewer points (appendix p 9). An example score form is shown in figure 3. Among 46 108 neonates from the development sample with complete data on the three variables included in the final model, 27 289 (59·1%) were designated as low risk, 17 215 (37·3%) as medium risk, and 1640 (3·6%) as high risk. Observed risks were 0·3% (95% CI 0·3–0·4) for low risk, 4·1% (3·8–4·4) for medium risk, and 27·3% (25·2–29·5) for high risk, with a c-index of 0·8875. Mean predicted risks derived from regression coefficients were 0·2% (SD 0·2) for low risk, 4·6% (SD 4·2) for medium risk, and 23·5% (SD 8·8) for high risk. Observed risks across population deciles by score were similar to the risks predicted with regression coefficients (appendix p 10).

After bootstrap resampling, optimism-adjusted estimates of c-index and Brier score were nearly identical to the original measures; thus, no adjustments were made to the coefficients. In the random validation sample, complete data on all three parameters were available for 35 193 (87·3%) of 40 329 neonates, for the temporal validation sample the data were available for 12 653 (85·4%) of 14 818 neonates, for the full validation sample they were available for 47 846 (86·8%) of 55 147 neonates, and for the Gambian validation sample complete data on all three parameters were available for 457 (83·1%) of 550 neonates. The model showed very good performance across the UK validation samples (c-index 0·8859–0·8930) and good performance in the Gambian validation sample (c-index 0·8170; Brier score 0·1688; table 4). Performance was similar among neonates weighing 1500 g or less in the Gambian sample (c-index 0·8069, Brier score 0·1753).

Graphical plots showed a high level of agreement between observed and predicted mortality risk across the external validation samples (figure 4). Applying the empirical optimal cutpoint of 3·9% based on the Youden Index gave moderately high sensitivity (79·1–81·6) and

specificity (81·0–82·9), with high negative predictive value (99·3) and low positive predictive value (11·4–12·2; appendix p 10).

The discriminatory ability of the simplified integer score was similar to the model using regression coefficients, with c-indices of 0·8903 in the full validation sample and 0·8082 in the Gambian validation sample (appendix p 11). Among the 47 846 neonates in the UK full validation sample, 28 565 (59·7%) were designated as low risk, 17 407 (36·4%) as medium risk, and 1874 (3·9%) as high risk. Observed risks for these categories were 0·4% (95% CI 0·3–0·5) for low risk, 4·8% (4·5–5·1) for medium risk, and 29·7% (27·7–31·8) for high risk. In the Gambian validation sample, the score range for low risk was set at 23 or more, for medium risk at 17–22, and for high risk at 16 or fewer points (appendix pp 3, 11). Among the 457 neonates in the Gambian sample for whom data on all three parameters were available, 28 (6·1%) were designated as low risk, 215 (47·1%) as medium risk, and 214 (46·8%) as high risk. Observed risks were 10·7% (95% CI 3·5–28·5) for low risk, 21·4% (16·4–27·4) for medium risk, and 68·2% (61·7–74·1) for high risk. Mean predicted risks derived from regression coefficients were 9·4% (SD 1·9) for low risk, 22·3% (SD 8·5) for medium risk, and 67·4% (SD 18·4) for high risk. Observed risks across population deciles by score were similar to those predicted with coefficients (appendix p 11).

Comparison of areas under the ROC curves for NMR-2000 (c-index 0·8523 [95% CI 0·8336–0·8710]) and CRIB-II (c-index 0·7443 [95% CI 0·7153–0·7733]) among 10 812 neonates born at 32 weeks' gestation or earlier (figure 5) indicated that discriminatory performance of NMR-2000 was superior to that of CRIB-II ($p<0·0001$).

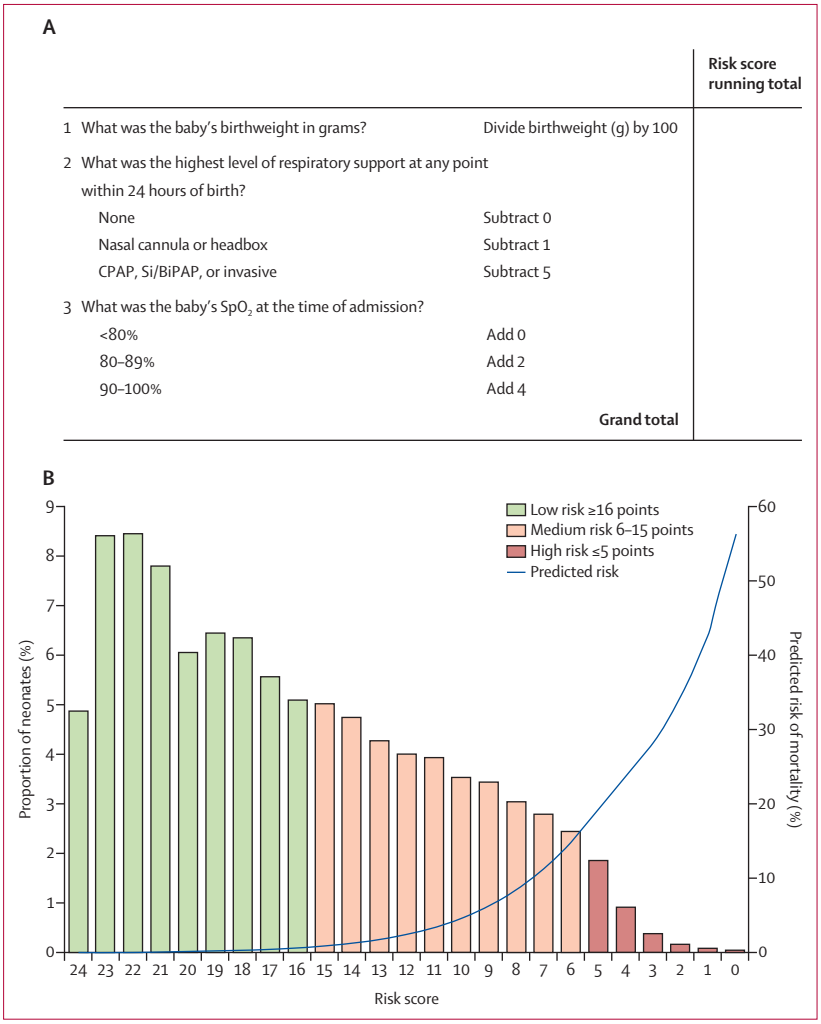

Figure 3: **NMR-2000, a simplified risk score to predict mortality amongst neonates weighing 2000 g or less**
(A) An example mortality risk score for clinical use. (B) Predicted risk of in-hospital mortality plotted against risk scores in the development sample; bar data indicate proportion of neonates; blue line indicates predicted mortality risk. CPAP=continuous positive airway pressure. BiPAP=bilevel positive airway pressure. SiPAP=synchronised intermittent positive airway pressure.

Discussion

This population-wide study, including data from 110 176 newborn babies at 187 hospitals in the UK and 550 newborn babies at one hospital in The Gambia, has derived and validated NMR-2000 for predicting in-hospital mortality. A strength of this work is that, to our knowledge, this is the largest dataset that has been used to develop and validate a neonatal mortality risk score. Among neonates born at 32 weeks' gestation or earlier, the discriminatory ability of NMR-2000 was superior to that of CRIB-II, one of the most widely used neonatal risk scores.

Performance of the NMR-2000 simplified integer score, which can be measured and calculated at the bedside, was similar to that of the model using regression coefficients. The three parameters used in the score can be feasibly collected in LMIC settings. Although sub-Saharan Africa and southern Asia account for 78% of the world's neonatal deaths,[1] existing risk scores have primarily been developed for intensive care settings and often require complex calculations. In LMICs, where parameters in widely used scores are typically not available nor reliably measurable,[20,21] NMR-2000 could support shared decision making by enabling providers to objectively assess illness severity.[29] The score could be used in clinical trials to assess eligibility and compare participants.[29] Additionally, NMR-2000 could inform service delivery planning by identifying bottlenecks in care provision.[6] Given that 73% of neonatal deaths occur within the first 7 days of life,[24] early recognition of severe illness and rapid initiation of evidence-based interventions are crucial to promoting survival.[5,9,12]

The c-index was 0·8859–0·8930 across the development and UK validation samples, suggesting that NMR-2000 can discriminate neonates who will die from neonates who will survive. This level of performance is similar to that of commonly used neonatal mortality scores in high-resource settings. Discriminatory ability at the time of model derivation ranged from 0·87 for TRIPS-II[16] to 0·92 for CRIB-II.[18] Similar to TRIPS-II, NMR-2000 can be

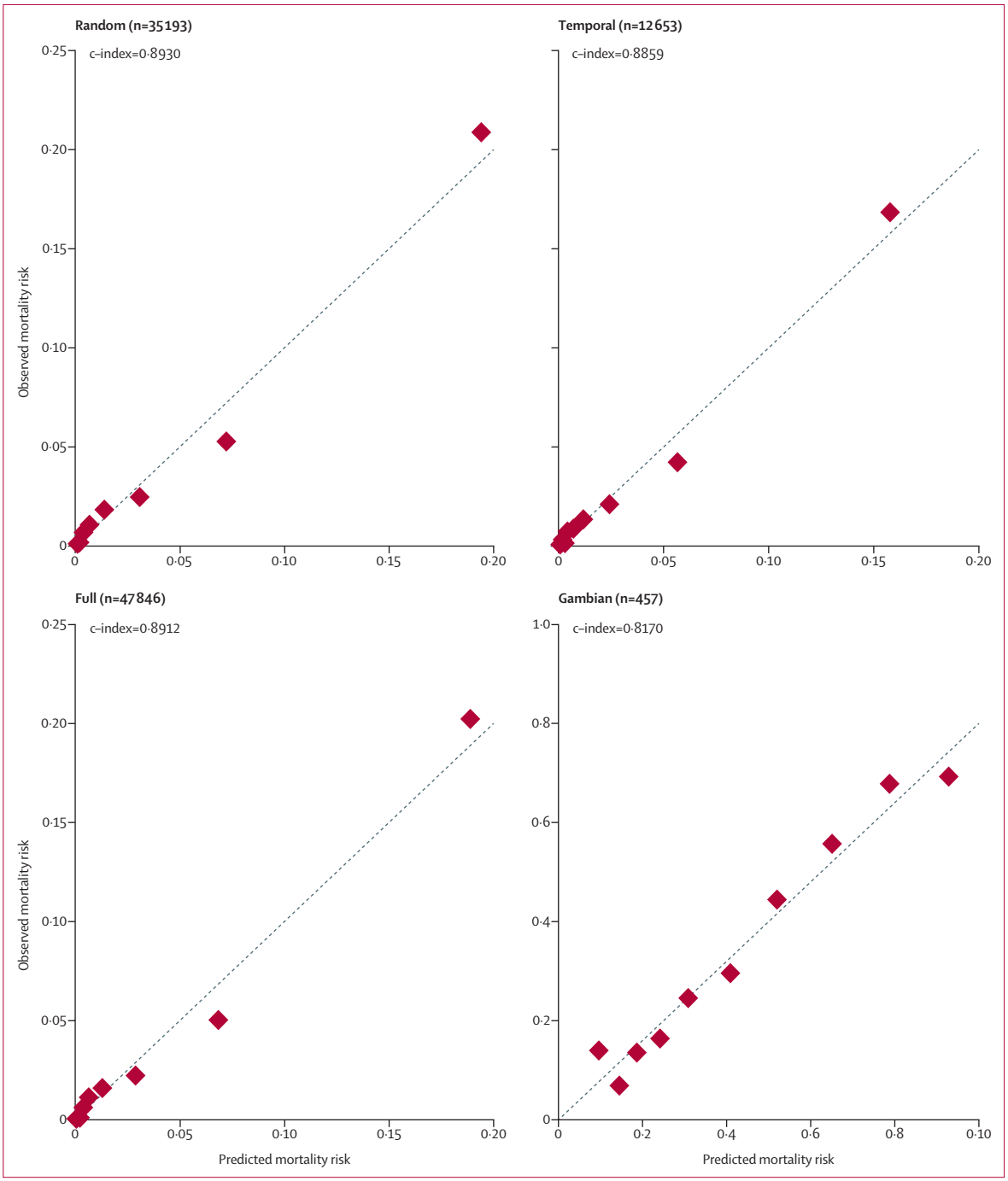

Figure 4: **Predicted versus observed mortality risk for population deciles in the random, temporal, full, and Gambian validation samples**
Graphs created using pmcalplot.

assessed at any point within the first 24 h of life and could be repeated if the level of respiratory support increases. The performance of NMR-2000 (c-index 0·8523) was superior to that of CRIB-II (0·7443) among neonates born at 32 weeks' gestation or earlier. The model also showed very good predictive ability for mortality within 24 h of birth (c-index 0·8858), which is notable because 37% of neonatal deaths in sub-Saharan Africa occur within this timeframe.[24] The NMR-2000 model showed a high level of agreement between observed and predicted deaths, as assessed by calibration plots, in the development and validation samples. Calibration plots are the preferred method for assessing calibration.[25] Previous neonatal scores, including NTISS,[13] SNAPPE-II,[15] CRIB-II,[18] and

TRIPS-II,[16] were reported to have good calibration for predicting in-hospital mortality using the Hosmer-Lemeshow test. However, such results should be interpreted with caution given the limitations of this test, which include subjective and imprecise grouping of babies as well as inability to denote the directionality of miscalibration when incongruities are detected.[25]

In the Gambian validation sample, the NMR-2000 model had good discrimination and overall goodness-of-fit, with c-index of 0·8170 and Brier score of 0·1688. Complete data were available for 83% of neonates. The calibration plot showed a strong agreement between observed and predicted mortality. These findings suggest that NMR-2000 is valid for use in LMIC settings where pulse oximetry is available. Discrimination of the SAWS score, developed for neonates weighing 1500 g or less in low-resource settings, at the time of validation (c-index 0·679–0·698)[22] was decreased relative to NMR-2000 among Gambian neonates weighing 1500 g or less (c-index 0·8069). Notably, neither goodness-of-fit nor calibration were reported for the SAWS score.[22] Further, SAWS relies on accurate assessment of gestational age, which can be challenging in LMICs because of late presentation for antenatal care, poor recall of last menstrual period, and unavailability of ultrasonography.[30] Case-fatality of Gambian neonates in this study is similar to that reported from a previous study at EFSTH (35% overall, 58% for neonates with a very low birthweight),[23] and higher than studies at similar hospitals in Ghana (20% overall),[31] Nigeria (14–20% overall),[32,33] and Burkina Faso (15% overall).[34]

Among the three NMR-2000 parameters, all except SpO_2 are included on routine admission forms at EFSTH, Gambia (at time of screening),[23] as well as standard forms at government hospitals in Kenya, Malawi, and Tanzania. We were able to obtain SpO_2 data for the Gambian sample primarily because these data were being collected as part of the eKMC trial screening process. Variability in the implementation of routine pulse oximetry is a crucial gap in low-resource neonatal units.[35,36] In a study of nearly 7500 neonates admitted to 11 hospitals in Nigeria, hypoxaemia increased the adjusted odds of mortality by six times, and clinical signs (eg, chest in-drawing, grunting) poorly predicted hypoxaemia.[37] Furthermore, expansion of neonatal inpatient care, often of variable quality and frequently inclusive of unmonitored 100% oxygen supplementation, has placed sub-Saharan Africa on the brink of an epidemic of retinopathy of prematurity.[38] Widespread availability of SpO_2 monitoring and improved coverage of screening for and treatment of retinopathy of prematurity will be essential to control the incidence of visual loss in affected neonates. In LMIC settings, successful implementation of NMR-2000 would require sensitisation around recording the three parameters. Several studies have highlighted issues surrounding the collection of data on neonatal care in LMICs, including variable uptake of standard admission forms;[36] incomplete documentation of assessments, monitoring, and therapies prescribed;[20,23,36] and low capacity of data systems to capture information on neonates who die soon after birth or are transferred to another facility.[4] Increasing the quality and coverage of data is crucial to promote actions to improve neonatal survival, and will require coordination across different levels of the health-care system.

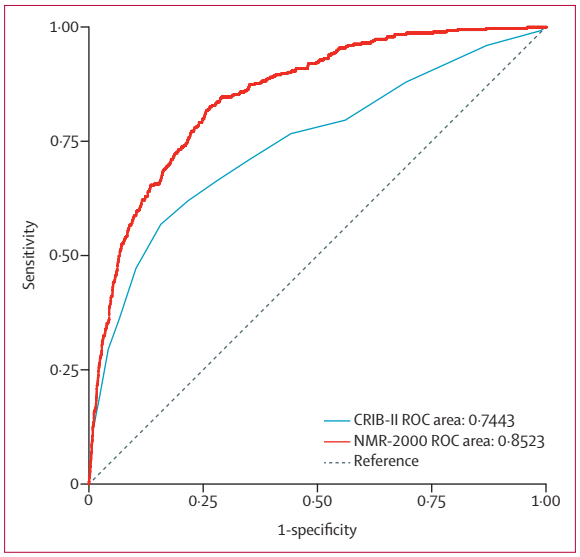

Figure 5: **Comparison of areas under the ROC curves for CRIB-II and NMR-2000**
This analysis includes neonates born at 32 weeks' gestation or earlier in the full validation sample (n=10 812). ROC=receiver operating characteristic.

One strength of this study is our use of a large and purposely-selected UK dataset, which enabled maximisation of model performance. One limitation is that the Gambian dataset was small and limited to a single hospital; research is required to validate the model using a larger LMIC dataset. Several candidate variables in the development sample had a considerable proportion of missing data, including admission heart rate, respiratory rate, and SpO_2. It was not possible to compare NMR-2000 with the CRIB, SNAP, SNAP-II, SNAPPE-II, or TRIPS-II scores, because the NNRD did not include all parameters required for their calculation. Because pulse oximetry is not always available in low-resource neonatal units, the usefulness of the NMR-2000 score in such settings could be limited. The NNRD did not include clinical signs of respiratory distress that could be tested as a potential proxy for SpO_2. We tested a related variable (clinically relevant increase in apnoea or bradycardia, oxygen requirement, ventilatory support, or respiratory rate); however, this variable was not associated with mortality. The use of respiratory support level as a parameter could affect the performance of the model. Administration of therapies varies in line with variations in clinical practice[19] and resource availability and so might not reflect true therapeutic requirements.[36] In LMICs, delivery systems for oxygen therapy and CPAP might be unavailable or non-functional, and related supplies (eg, nasal cannulas) might be out of stock.[8,35,36]

Research is required to validate the NMR-2000 score in low-resource settings using a sufficiently sized dataset, and to evaluate its usefulness for supporting clinical decision making.[29] A follow-up study using a large, multihospital dataset from Kenya is planned. Nurses have essential roles as frontline providers of neonatal care; however, there is a severe shortage of neonatal nurses in LMICs.[6,7] Future research could explore the model's ability to inform resource use,[13] particularly nursing workload.

The NMR-2000 is a simplified risk score, validated for high-resource and low-resource settings where pulse oximetry is available, to accurately predict in-hospital mortality among neonates weighing 2000 g or less. By enabling providers to objectively assess illness severity, this tool could contribute to improvements in the quality of care delivered in LMIC facilities. Early recognition of severe illness and rapid initiation of evidence-based interventions are crucial to promoting survival of small and vulnerable neonates.

Contributors

MMM, CT, DE, JEL, and EA conceived the study. MMM, HB, CT, DE, JEL, and EA contributed to study design. MMM and EA developed the analysis plan. MMM, CT, and CG were involved in curation of data from the NNRD. HB and AG collected data in The Gambia. MMM analysed the data and wrote the manuscript. MMM, HB, CT, CG, PW, DE, JEL, and EA interpreted the data. All authors participated in manuscript revision and approval of the final version.

Declaration of interests

CG has received grants from the Medical Research Council during the conduct of the study; grants from the National Institute for Health Research, Mason Medical Research Foundation, Chiesi Pharmaceuticals, Rosetrees Foundation, and the Canadian Institute for Health Research, outside the submitted work; and personal fees from Chiesi Pharmaceuticals, outside the submitted work. CG is also a voluntary, unremunerated member of the Neonatal Data Analysis Unit Steering Board, which oversees the UK National Neonatal Research Database. JEL is a member of the International Advisory Board for *The Lancet Child and Adolescent Health*. All other authors declare no competing interests.

Data sharing

Data from the UK National Neonatal Research Database is available upon request.

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5. Current evidence regarding duration, timing, clinical impact, and causal pathways for clinical effects of kangaroo mother care: literature review

5.1. Scope of this chapter

Chapter 5 presents current evidence regarding the practice of KMC, including recommended duration and time of initiation (section 5.2), findings of relevant meta-analyses (section 5.3), and a literature review of RCTs examining the effect of KMC on mortality, LOS, and hypothermia (section 5.4). Existing evidence regarding potential causal pathways for the beneficial effects of KMC on mortality and other important clinical outcomes is also presented (section 5.5).

5.2. KMC duration and time of initiation

5.2.1. Current WHO recommendations

WHO guidelines for preterm care recommend KMC for the "routine care of newborns weighing ≤2000g… initiated as soon as newborns are clinically stable."[44] The WHO *Practical Guide to KMC* states that KMC should begin gradually, increasing to as close to continuous as possible.[8]

5.2.2. KMC duration

The optimal duration of KMC is unknown, and data are needed to understand the dose-response relationship between KMC duration and mortality.[43] This must be balanced with the practicality of providing KMC for extended periods of time.[62] Studies have shown that continuous KMC can be difficult to achieve; mothers may find it overwhelming, and clinicians and administrators may be unaware of the need for near-continuous provision.[67] Adherence may be improved by educating clinicians and administrators, and providing comfortable beds, gowns, and KMC wraps for caregivers.[67]

5.2.3. KMC time of initiation

The optimal time of initiation of KMC is also unknown. In an RCT comparing early-onset (<24h) to late-onset (24-72h) KMC in relatively stable infants in Madagascar, the early-onset group had a non-statistically significant increase in neonatal mortality. However, there were no differences in the incidence of morbidities, adverse events, or LOS between the two groups.[68]

5.3. Effect of KMC on mortality and other clinical outcomes: evidence from meta-analyses

The most recent Cochrane review (2016) demonstrated that KMC is associated with decreased mortality [relative risk (RR) 0.60, 95% confidence interval (CI) 0.39-0.92 (8 trials)], sepsis [RR 0.35, 95% CI 0.22-0.54 (5 trials)], and hypothermia [RR 0.28, 95% CI 0.16-0.49 (9 trials)] at discharge or 40-41 weeks postmenstrual age, compared to conventional care amongst stable neonates ≤2000g.[42] A meta-analysis by Boundy et al (2016) found that KMC is associated with decreased mortality at latest follow-up among infants <2000g [RR 0.64, 95% CI 0.46-0.89 (15 studies)], sepsis [RR 0.53, 95% CI 0.34-0.83 (8 studies), hypothermia [RR 0.22; 95% CI 0.12-0.41 (9 studies), and hypoglycaemia [RR 0.12; 95% CI 0.05-0.32 (2 studies)].[43]

5.4. Literature review of RCTs examining the effect of KMC on mortality, length of stay, and hypothermia

5.4.1. Methods

The objective of this literature review was to inform the planned RCT aiming to determine the effect of KMC initiated before stabilisation on mortality and other important clinical outcomes relative to standard care amongst newborns ≤2000g. This review was conducted prior to my PhD upgrade in November 2016. I searched MEDLINE/PubMed, Embase, and Google Scholar for studies published from inception through October 31, 2016. The search strategy is described in further detail in Annex A.5. Trials were included if they met all of the following criteria: 1) randomised (individually or in clusters), 2) KMC compared with standard care (incubator, radiant warmer, or late-onset KMC), 3) enrolled LBW infants, 4) mean/median enrolment <15d post-birth, 5) reported mortality, LOS, or hypothermia as outcomes. Trials were excluded if they met any of the following criteria: 1) non-randomised or quasi-randomised, 2) enrolled infants with birthweight ≥2500g and did not separately report those results, 3) crossover design, 4) mean/median enrolment ≥15d post-birth, 5) did not report mortality, LOS, or hypothermia as outcomes. Notably, these eligibility criteria are more specific than those utilised in the aforementioned meta-analyses; for example, the Cochrane review included trials that initiated KMC at ≥15 days post-birth,[42] and the meta-analysis by Boundy et al included both randomised and non-randomised studies.[43] To identify relevant ongoing RCTs, I searched several clinical trial registries most recently in October 2019 using the terms, “kangaroo care” and “skin-to-skin contact” (see Annex A.5 for further details).

5.4.2. Results

Fifteen trials, which included 2698 infants, met inclusion criteria. Table 5-1 summarises the characteristics of infants enrolled in the included RCTs, including the definition of clinical stability (if provided) and the percentage of LBW infants who were eligible.

Table 5-1. Characteristics of infants in RCTs included in the review

Study	Inclusion criteria	Exclusion criteria	Mean/median age at time of enrolment	Clinical stability definition	Size, percent LBW infants eligible
Acharya 2014[69]	Stable, BW <2000g, admitted to newborn unit	Unstable, chromosomal or life-threatening congenital anomalies, mother ill or did not give consent	Not provided	Not requiring ventilatory or inotropic support or radiant warmer	126 infants; 87%
Ali 2009[70]	Stable, delivered vaginally, BW 1200-1800g	Delivered by caesarean section, life-threatening congenital malformations, severe perinatal complications, parents refuse KMC	4.7d ± 2.9 in KMC group 4.8d ± 2.4 in control group	'Hemodynamically stable'	114 infants, 81%
Cattaneo 1998[71]	Stable, BW 1000-1999g, ability to partially feed, mother present and willing to collaborate	No visible major malformation	10 (1-74) days in KMC group 8 (1-40) days in control group	Not requiring oxygen or IV fluids	285 infants, 44%
Charpak 1997[72]	Stable, BW ≤2000g, sucks and swallows well, weight gain, mother/relative able to understand/follow instructions	Referred, plans to leave Bogotá in near future, life-threatening or major malformations, major conditions arising from perinatal problems, parental/ family refusal to follow-up, refusal to comply with KMC in intervention group	4d (1-60) in KMC group 3d (1-55) in control group	Recovered from "major problems of adaptation to extra-uterine life," treated for infection and/or concomitant condition	777 infants, 72%
Eka Pratiwi 2009[73]	Stable, BW 1500-2250g, Apgar score >6 at 5min, mother willing to follow instructions	Major congenital malformations, cardio-pulmonary problems, critical illness (sepsis, NEC, ICH); twin gestation, complicated pregnancy/labour; maternal history of drug abuse, psychiatric disorders, or caesarean section, or inability to care for self or baby	<1d	Not defined	93 infants, 37%

Study	Inclusion criteria	Exclusion criteria	Mean/median age at time of enrolment	Clinical stability definition	Size, percent LBW infants eligible
Gathwala 2008[74]	Stable, BW ≤1800g, Apgar score ≥7 at 1 and 5min, tolerating enteral feeds, maintaining temperature	Infant sick, unstable, or with major congenital malformations; mother unwell or refused consent	1.7d ± 0.5	'Stable cardio-pulmonary status'	110 infants, no data on percent of LBW infants eligible
Ghavane 2012[75]	Stable, BW ≤1500g, tolerating feeds of 150 mL/kg/d	Major malformations, parents refuse consent	14.1d ± 10.3 in KMC group 13.7d ± 10.2 in control group	Not receiving IV fluids, oxygen or respiratory support, no apnoea for 72h	140 infants, no data on percent of LBW infants eligible
Kadam 2005[76]	Stable, BW ≤1800g, Apgar score ≥7 at 5min, enteral feeds	Infant sick and unstable, major congenital malformations; parents refuse consent	3.2d (1-8)	'Stable cardio-pulmonary status'	89 infants, no data on percent of LBW infants eligible
Kumbhojkar 2016[77]	Stable, BW <2000g	Infant critically ill requiring ventilatory or inotropic support; chromosomal or life-threatening congenital anomaly; mother ill; unable to follow-up	3d in KMC group 4d in control group	Requiring ventilatory or inotropic support	120 infants, 52%
Nagai 2010[68]	Relatively stable, BW <2500g, age <24h, mother or other family healthy and willing to practice KMC	Serious malformation, prolonged apnoea (>20 sec), IV infusion	19.8h in early-onset group, 33.0h in late-onset group	SpO_2 ≥95%, HR >100 bpm, RR <60 breaths per min, capillary refill time <3 sec	73 infants, 52%
Nimbalkar 2014[78]	Stable, delivered vaginally, BW ≥1800g	Infant delivered by caesarean section; requiring resuscitation; congenital anomaly	43 ± 13min in KMC group 30-60min in control group	Not defined	100 infants (45 LBW), 43% of all screened infants eligible
Ramanathan 2001[79]	Stable, BW <1500g, tolerating enteral feeds, maintaining temperature in thermoneutral environment	Mother unable to come to nursery due to illness or disability	Not provided	'Stable cardio-pulmonary status'	28 infants, no data on percent of LBW infants eligible
Sloan 1994[80]	Stable 24h prior to enrolment, singleton, BW <2000g, tolerating enteral feeds, stable weight	No serious congenital abnormalities or respiratory, metabolic, or infectious disease	13.0d ± 10.5	Temperature 36.5-37.0°C	300 infants, 53%
Suman Rao 2008[81]	Stable, singleton, BW <2000g	Infant critically ill requiring ventilatory or inotropic support, chromosomal and life-threatening congenital anomalies, transfer; mother ill or unable to follow-up	3.7d ± 2.8 in KMC group 2.3d ± 1.9 in control group	Not requiring ventilatory or inotropic support	220 infants, 63%

Study	Inclusion criteria	Exclusion criteria	Mean/median age at time of enrolment	Clinical stability definition	Size, percent LBW infants eligible
Worku 2005[60]	Unstable, BW <2000g, singleton unless 1 twin died; mother healthy and willing to participate	No major congenital malformations	10.0h in KMC group 9.8h in control group	Stable temperature and cardiovascular status, ability to suck, good general condition	123 infants, 48%

LBW=low birthweight; BW=birthweight; IV=intravenous; NEC=necrotising enterocolitis; ICH=intracranial haemorrhage; HR=heart rate; RR=respiratory rate

Amongst the fifteen RCTs included in the review, there was significant variability in how clinical stability was defined. Six defined this based on therapies,[69,71,72,75,77,81] five on 'hemodynamic stability,'[60,70,74,76,79] and one on vital sign parameters.[68] Three RCTs did not report a definition for stability.[73,78,80]

Table 5-2 provides a description of the RCTs included in the review, including interventions provided in the standard care group, timing and duration of KMC in the KMC group, and outcomes assessed.

Table 5-2. Description of RCTs included in the review

Study	Setting (country, facility type)	Standard care group	Continuous or intermittent KMC, initiation time (if provided)	Median duration KMC per day	Outcomes
Acharya 2014[69]	Nepal; newborn nursery at tertiary care hospital	Radiant warmer only	Intermittent	≥6h	Weight/length/HC gain, hypothermia, apnoea, LOS
Ali 2009[70]	India; NICU at tertiary care hospital	Radiant warmer or open cot in warm room	Intermittent	6.3h ± 1.52	LOS, weight/HC/length gain, BF, nosocomial sepsis, hypothermia, infection, mortality
Cattaneo 1998[71]	Ethiopia, Mexico, and Indonesia; neonatal units at academic hospitals	Radiant warmer or open crib in warm room (Ethiopia); incubator (Mexico, Indonesia)	Continuous	≥20h	Mortality, severe illness, weight gain, hypothermia, hyperthermia, BF, acceptability to health workers and mothers, cost
Charpak 1997[72]	Colombia; KMC ward or NICU of tertiary care hospital	Incubator only until able to regulate temperature and thriving	Continuous	≥20h	Mortality, LOS, infection, growth (weight, length, HC), breastfeeding, mother-infant attachment
Eka Pratiwi 2009[73]	Indonesia; NICU at public hospital	Incubator or open cribs in warm rooms	Intermittent; initiated on day of birth	10.0h ± 1.8 (range 5.3-13.5)	Hypothermia, BW regain, sepsis, mortality

Study	Setting (country, facility type)	Standard care group	Continuous or intermittent KMC, initiation time (if provided)	Median duration KMC per day	Outcomes
Gathwala 2008[74]	India; neonatal unit at academic hospital	Incubator or radiant warmer	Intermittent; initiated at mean 1.72d ±0.45	10.2h ± 1.5 in first month	Mother-infant attachment; LOS, BF, weight/length/HC gain
Ghavane 2012[75]	India; KMC ward or intermediate care unit of tertiary care hospital	Incubator or radiant warmer	Intermittent	≥8h, placed in open cribs when not in KMC	Weight/length/HC gain, BF, LOS, hypothermia, sepsis, apnoea, hypoglycaemia
Kadam 2005[76]	India; NICU at tertiary care hospital	Radiant warmer only	Intermittent	9.8h ± 3.7	Mortality, hypothermia, hyperthermia, sepsis, apnoea, breastfeeding, LOS, weight gain
Kumbhojkar 2016[77]	India; NICU at university hospital	Radiant warmer only	Intermittent	11.5h, temporarily withdrawn from KMC if life-threatening event or needed phototherapy	Weight/length/HC gain; LOS; hypothermia; sepsis; apnoea; acceptability; BF
Nagai 2010[68]	Madagascar; neonatal unit at academic hospital	Late-onset KMC (post-stabilisation, 24-72h)	Continuous; initiated within 24h	Not provided	Mortality, severe infection, re-admission, hypothermia, hyperthermia, BF, bradycardia or tachycardia, prolonged apnoea, weight gain, LOS, discharge ≤7d
Nimbalkar 2014[78]	India; maternity ward	Radiant warmer only	Intermittent; initiated within 1h post-delivery	17.0h ± 0.3 during first 24h; KMC was discontinued at 24h	Hypothermia
Ramanathan 2001[79]	India; NICU at tertiary care hospital	Incubator or radiant warmer	Intermittent	≥4h	Weight gain, BF, LOS
Sloan 1994[80]	Ecuador; NICU at maternity hospital	Incubator or radiant warmer	Continuous	≥20h	LOS, readmission, cost, septicaemia, pneumonia, lower/ upper respiratory tract infection, urinary tract infection, jaundice, apnoea, aspiration, diarrhoea, dermatitis, growth (weight, length, HC, upper arm), hip displacement
Suman Rao 2008[81]	India; NICU at tertiary care hospital	Radiant warmer only	Intermittent	13.5h with mean total duration 33.8d ± 15.1	Mortality, hypothermia, hyperthermia, sepsis, LOS, hypoglycaemia, apnoea in <1500g, growth (weight, length, HC, chest, mid-arm, foot length)

Study	Setting (country, facility type)	Standard care group	Continuous or intermittent KMC, initiation time (if provided)	Median duration KMC per day	Outcomes
Worku 2005[60]	Ethiopia; neonatal unit at academic hospital	Radiant warmer only	Continuous; initiated within 24h	Not provided	Mortality, sepsis, diarrhoea, pneumonia, aspiration, mothers' feeling about KMC

HC=head circumference; LOS=length of stay; NICU=neonatal intensive care unit; BF=breastfeeding; BW=birthweight

Among the seven RCTs evaluating mortality, five reported decreased mortality (RR 0.20-0.98)[60,71,72,80,81] while two reported increased mortality (RR 1.02-1.95).[68,76] However, both which found increased mortality had very few deaths (Nagai, 2 vs. 1; Kadam, 1 vs. 1) and neither reached statistical significance. The only RCT enrolling neonates before stabilisation reported major mortality reduction (RR 0.57); however, 66% of deaths and the major difference between arms occurred within 12 hours of birth.[60] Among the eleven RCTs reporting LOS, eight found infants in the KMC group had decreased LOS (mean difference 0.8-7.4 days),[68,70,72,74–77,79] two found increased LOS (mean difference 0.5-3 days),[69,80] and one found no difference.[81] Among the nine RCTs reporting incidence of hypothermia, seven found infants in the KMC group had decreased hypothermia (RR 0.10-0.58)[69,70,73,76–78,81] and two found no difference.[68,75]

In addition to the trials included in the review, three related RCTs are ongoing. The 'Early KMC' (eKMC) trial is evaluating the effect of KMC initiated within 24h relative to standard care (including KMC at >24h) on neonatal mortality amongst moderately stable newborns <2000g in The Gambia.[82] The 'Immediate KMC' (iKMC) trial will compare the impact of KMC initiated within 2h of birth relative to standard care on mortality within 72h and 28 days amongst newborns 1000 to <1800g at five national referral hospitals (Ghana, India, Malawi, Nigeria, Tanzania), where intensive care resources including CPAP are available.[83] The 'Immediate Parent-Infant Skin-to-Skin Study' (IPISTOSS) is comparing the effect of continuous SSC initiated within 1h of birth relative to standard care on cardiorespiratory stability at 6h amongst neonates born at ≥28 to <33 weeks gestational age at three university hospitals in Sweden and Norway.[84]

5.5. Potential causal pathways for clinical effects of KMC

5.5.1. Thermal control and risk of intraventricular haemorrhage

A variety of underlying mechanisms may be responsible for the beneficial effects of KMC on mortality and other important outcomes, many of which are mediated by SSC between the baby

and caregiver. Numerous studies have reported improved thermal control with KMC,[49,69,70,76–78,81,85] whilst two found no difference in the incidence of hypothermia.[68,75] In a study of 34 neonates receiving mechanical or nasal CPAP ventilation in the Netherlands, neonates 25 to <27 weeks gestational age had a mean skin temperature decrease of 1.1% during SSC and 1.4% after SSC.[86] Neonates 27 to <30 weeks gestational age had a decrease of 0.5% during SSC, which was not statistically significant, and a decrease of 0.8% after SSC. They concluded that SSC is safe for ventilated neonates <30 weeks gestational age, "as long as skin temperature is monitored and extra warmth is provided if necessary."[86] In a population-based study of 8,782 VLBW neonates in California, moderate hypothermia (32.0-35.9°C) was associated with increased odds of severe intraventricular haemorrhage (IVH, grade 3 or 4) on or before 28 days (odds ratio 1.3, 95% CI 1.1-1.6).[87] Hence, thermally-mediated reduction in the risk of severe IVH may represent a novel causal pathway for the protective effect of KMC, particularly among VLBW newborns.[87]

5.5.2. Brain maturation and neurophysiologic organisation

A growing body of evidence suggests that KMC may accelerate brain maturation and improve neurophysiologic organisation in preterm neonates. Maturation of circuitry in the somatosensory system, which is indicated by the appearance of evoked brain activity together with the departure of spontaneous burst activity on electroencephalogram (EEG), occurs at 35-37 weeks' gestation.[88] In line with this, a study found that preterm infants exhibited attenuated brain responses to light touch at the time of NICU discharge relative to term controls, and that SSC was associated with increased amplitude of touch responses in preterm infants.[89] A study of former LBW infants who participated in a KMC trial in Colombia 20 years earlier demonstrated increased volume of the left caudate nucleus in the KMC group.[90] This is notable since several studies have shown reductions in basal ganglia and thalamic (Figure 5-1) volumes among preterm infants at term-equivalence,[91–94] including one that reported a 10% reduction in caudate nucleus size among infants <30 weeks gestational age relative to term controls.[94] Larger basal ganglia volumes in preterm infants at term-equivalent age are associated with improved motor functioning in childhood,[94,95] as well as higher intelligence quotient and academic outcomes at age 7 years.[94,96] The latter could be explained by an increased distribution of dopamine receptors in the caudate nucleus,[97] leading to improved motivational control of learning and reward-seeking behaviours.[98]

Figure 5-1. Segmentation of basal ganglia nuclei and thalamus in a term infant

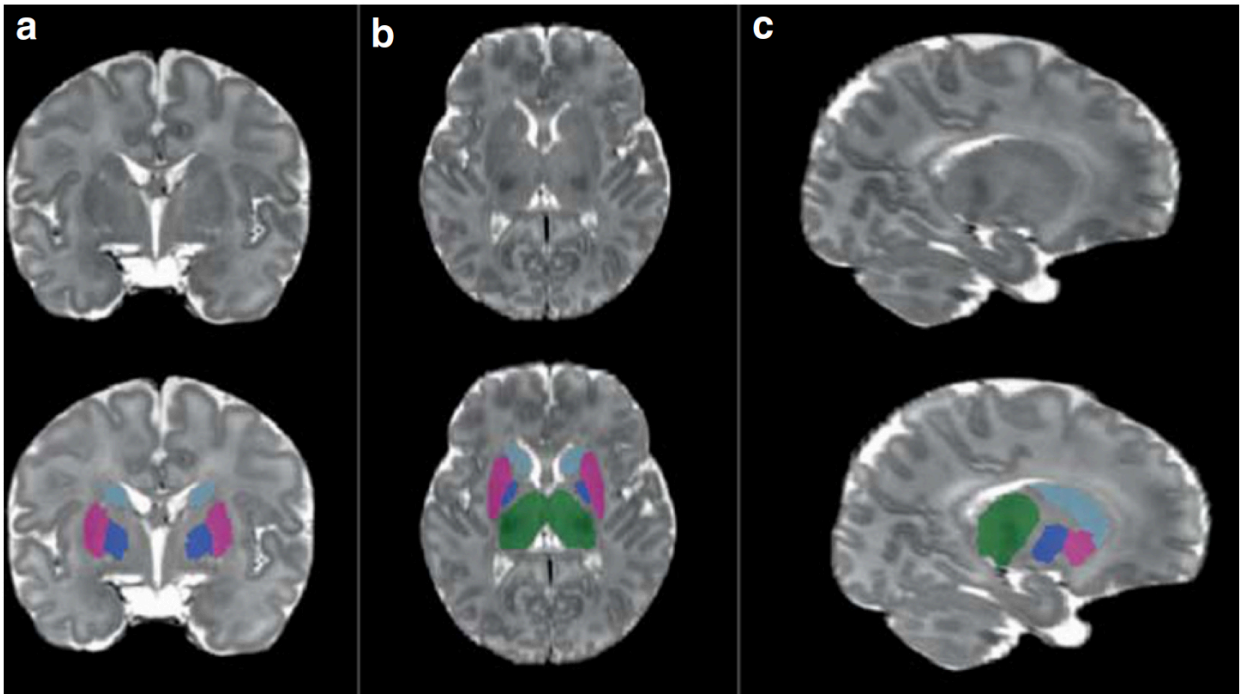

Image source: Loh et al., 2017.[94] Magnetic resonance images of basal ganglia and thalamus in (a) coronal, (b) axial, and (c) sagittal views. Light blue = caudate nucleus; dark blue = pallidum; fuchsia = putamen; green = thalamus.

Preterm birth interrupts the normal sequence of brain development, and affected neonates may display disorganised sleep, reduced autonomic functioning, and increased reactivity of the hypothalamic-pituitary-adrenal (HPA) axis to stress.[99–102] An American study reported that preterm neonates who received SSC exhibited more quiet sleep, improved respiratory regularity, and longer sleep cycles relative to term and term-equivalent controls.[99] In a later paper, the same group showed that preterm neonates who received SSC had increased EEG sleep complexity relative to the non-SSC preterm group at the same postmenstrual age. Discriminant analysis showed that SSC neonates at term-equivalent age were closer to the non-SSC term group than to the non-SSC preterm group at the same age, suggesting that SSC accelerated neurophysiologic maturation.[100] Similarly, a study in Israel showed that preterm infants receiving SSC 1h/d for ≥14 days exhibited longer periods of quiet sleep and alert wakefulness; shorter periods of active sleep; higher orientation and habituation scores on the Neonatal Behavioural Assessment Scale; and accelerated maturation of vagal tone between 32 and 37 weeks.[101] A subsequent Israeli study showed that children who received SSC displayed increased autonomic functioning at term-equivalent age as well as reduced stress reactivity, improved autonomic functioning, more organised sleep, and better cognitive control by 10 years of age.[102]

5.5.3. Cardiorespiratory stability

In line with the above findings regarding enhanced autonomic functioning, numerous studies in high- and middle-income settings have suggested that KMC improves cardiorespiratory stability.[50,103–106] This may be related to attenuation of stress reactivity,[107,108] potentially mediated by parent-baby oxytocin release during SSC.[109] In Canada, a randomised crossover trial of 61 neonates born at 28-31 weeks' gestation and aged <10 days found that infants receiving SSC 15 minutes before and during heel stick had lower Premature Infant Pain Profile (PIPP) scores at 90 seconds post-procedure and faster recovery times relative to babies receiving incubator care.[103] The PIPP is a composite pain measure based on facial actions and changes in maximum heart rate and minimum SpO_2 from baseline.[103] Similarly, an American crossover trial of 14 newborns 30-32 weeks gestational age within 9 days of birth reported that babies receiving SSC had lower heart rates at baseline and during heel stick, and reduced heart rate variability during recovery.[104] Two related RCTs in Vietnam and South Africa found that LBW babies receiving SSC had improved cardiorespiratory stability within 6h of birth relative to babies receiving standard care.[50,105] In both, stability was evaluated using the Stability of the Cardio-Respiratory system in Premature infants (SCRIP) score, a composite measure based on assessment of heart rate, respiratory rate, and SpO_2 over a 5-minute period.[110] An American study of 38 neonates born at 27-30 weeks' gestation, who weighed 1000 to <1500g and were receiving nasal CPAP or nasal cannula flow, found that the group receiving SSC 2h/d had fewer bradycardic and oxygen desaturation episodes during SSC relative to time spent in incubator care between days 5-10 post-birth.[106] The SSC group also had fewer bradycardic and desaturation events relative to the standard care group.[106] Conversely, a German study of 22 spontaneously breathing neonates born at <32 weeks' gestation, with a mean chronological age of 26 days, found that the combined frequency of bradycardia and hypoxaemia increased from 1.5/h before to 2.8/h during SSC.[111] A follow-up study reported that the total rate of bradycardia and desaturation was higher during SSC (median 3.0/h) relative to incubator care following SSC, with ambient temperature elevated by 1°C (1.7/h).[112] Notably, babies in these two studies were positioned at a 15–30° angle during SSC,[111,112] whereas those in the aforementioned American study were held upright (45-60° angle).[106] The authors suggested that upright positioning may reduce the risk of obstructive sleep apnoea,[106] which is more prevalent in preterm infants;[113,114] however, further research is needed to confirm this theory.

5.5.4. Breastmilk feeding and microbiome maturation

Other causal pathways for KMC may be mediated by SSC as well as breastmilk feeding. RCTs in stable neonates have demonstrated that KMC is associated with improved daily weight gain[69–71,74,79,81] and decreased incidence of sepsis/severe infection[70,72,77,81] at latest follow-up. Through both SSC and promotion of breastmilk feeding, KMC may stimulate lactogenesis and increase milk production,[115,116] facilitating weight gain and overall growth. A growing number of studies have suggested that KMC may promote maturation of the oral and intestinal microbiome in preterm neonates, stimulating colonisation of bacterial flora that may be protective against infection.[117–120] Further research is needed to understand the unique contributions of breastmilk feeding and SSC to microbiome establishment in this population.

5.6. Analysis of existing evidence

Major evidence gaps include the effect of KMC initiated prior to stabilisation on mortality and other important outcomes;[37,43,62] a clear, consistent definition of stability; the optimal time for KMC initiation; and the minimum duration required to reduce mortality. In addition, few studies have systematically examined causal pathways by which KMC may affect outcomes, particularly before stabilisation. Potential mechanisms include improved thermal control;[49,69,70,77,81,85] reduced IVH risk;[87] enhanced cardiorespiratory stability;[50,101,103–106] attenuation of the stress response;[107–109] increased breastmilk production;[115,116] and accelerated preterm microbiome maturation.[117–120]

6. Kangaroo Mother Care for clinically unstable neonates: is it feasible at a hospital in Uganda? (Paper C)

6.1. Scope of this chapter

Chapter 6 presents the third research paper entitled, "Kangaroo Mother Care for clinically unstable neonates: is it feasible at a hospital in Uganda?" This paper presents the findings of a feasibility study conducted at Jinja Regional Referral Hospital in Uganda to inform the design of a randomised trial to investigate the mortality impact of initiating KMC among newborns who are not yet stabilised. The study aimed to determine the proportion of admitted neonates meeting the proposed therapy-based criteria for instability; assess the feasibility of monitoring and providing care therapies to unstable neonates in the KMC position; and evaluate the acceptability of this intervention among newborn care providers and parents of hospitalised neonates.

This work was published in *Journal of Global Health* as an open access article in June 2018. See Appendix A.6.1 for the copyright. The paper was part of a six-paper supplement entitled 'Accelerating kangaroo mother care,' which also included papers focusing on service readiness for KMC and inpatient newborn care, tracking KMC implementation and coverage, community perspectives on KMC in Malawi, and a systematic review of the KMC literature.

In addition to the results presented in the paper, this study informed trial design by testing the proposed instability criteria (defined as receiving ≥2 therapies) and facilitating estimation of the number of eligible participants and the recruitment rates that would be required to achieve the target sample. Among neonates who received only one therapy, the majority received empiric antibiotics because they were at risk of infection, i.e., not for confirmed or suspected infection. This is a common practice in preterm/LBW newborns, including those who are considered stable. For this reason, the instability criterion for the trial was modified to receipt of ≥1 therapy excluding empiric antibiotics. The audit demonstrated that 89% of admitted neonates met the proposed instability criteria. Based on unpublished data from the Uganda Paediatric Association showing that approximately 480 neonates weighing ≤2000g are admitted annually, these findings suggest that ≥400 neonates would be eligible each year at Jinja Hospital.

The study further informed trial design by exploring provider and parental willingness to randomise small and sick newborns within the first 48h of birth. Interview findings indicated that all providers and parents were eager to participate in trials. Eighty percent of providers and 50%

of parents expressed willingness to randomise neonates. Among parents who were unwilling, most had stabilised newborns who were already receiving KMC, suggesting that these parents may be more open to randomisation before stabilisation when neonates normally receive incubator care. Providers expressed confidence that most parents would be amenable with thorough counselling.

Figure 6-1. KMC feasibility study training at Jinja Regional Referral Hospital, Uganda, 2016

Study team and newborn unit staff at Jinja Hospital

Supplies and equipment for feasibility study

6.2. List of figures

6.3. List of tables

6.4. Citation

Morgan M, Nambuya H, Waiswa P, Tann C, Elbourne D, Allen E, Lawn J. **Kangaroo Mother Care for clinically unstable neonates: is it feasible at a hospital in Uganda?** *J Glob Health* 2018; 8(1):010701. doi: 10.7189/jogh.08.010701.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	131393	**Title**	Dr
First Name(s)	Melissa Morgan		
Surname/Family Name	Medvedev		
Thesis Title	Informing the design of a trial of kangaroo mother care initiated before stabilisation amongst small and sick newborns in a sub-Saharan African context using mixed methods		
Primary Supervisor	Elizabeth Allen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	The Journal of Global Health as: Morgan MC, Nambuya H, Waiswa P, Tann C, Elbourne D, Seeley J, Allen E, Lawn JE. Kangaroo mother care for clinically unstable neonates weighing ≤2000 g: Is it feasible at a hospital in Uganda? J Glob Health. 2018; 8(1): 010701. doi: 10.7189/jogh.08.010701.		
When was the work published?	June 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not applicable		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I led the design of the study, with input from Drs Peter Waiswa and Cally Tann, and Profs Diana Elbourne, Janet Seeley, Elizabeth Allen, and Joy Lawn. I designed the data collection tools, with input from Dr Harriet Nambuya and Profs Diana Elbourne and Janet Seeley. I supervised data collection and I conducted all analyses. I wrote the first draft of the manuscript and prepared all subsequent revisions with consideration of comments from co-authors. See Annex A.1. for full details.

SECTION E

Student Signature	Melissa Medvedev
Date	10th October 2019

Supervisor Signature	Elizabeth Allen
Date	11/10/19

journal of global health

Kangaroo mother care for clinically unstable neonates weighing ≤2000 g: Is it feasible at a hospital in Uganda?

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Background Kangaroo mother care (KMC) for *stable* neonates ≤2000 g (g) is associated with decreased mortality, sepsis, hypothermia, and length of stay compared to conventional care. The World Health Organization states that KMC "should be initiated… as soon as newborns are *clinically stable*" [12]. However, the majority of deaths occur in *unstable* neonates. We aimed to determine the proportion of admitted neonates meeting proposed instability criteria, assess the feasibility of providing KMC to unstable neonates, and evaluate the acceptability of this intervention to parents and providers at Jinja Regional Referral Hospital in Uganda.

Methods This was a mixed-methods study. We recorded data including birthweight, chronological age, and treatments administered from medical charts, and calculated the percentage of clinically unstable neonates, defined as the need for ≥2 medical therapies in the first 48 hours of admission. We enrolled a sample of neonates meeting pre-defined instability criteria. Mothers were counselled to provide KMC as close to continuously as possible. We calculated the median duration of KMC per episode and per day. To explore acceptability, we conducted semi-structured interviews with parents and newborn unit care providers, and analysed data using the thematic content approach.

Findings We included 254 neonates in the audit, 10 neonates in the feasibility sub-study, and 20 participants in the acceptability sub-study. Instability criteria were easily implementable, identifying 89% of neonates as unstable in the audit. The median duration of individual KMC episodes ranged from 115 to 134 minutes. The median daily duration ranged from 4.5 to 9.7 hours. Seventy-five percent of interviewees felt KMC could be used in neonates concurrently receiving other medical therapies. Barriers included lack of resources (beds/space, monitoring devices), privacy issues, inadequate education, and difficulties motivating mothers to devote time to KMC. Recommendations included staff/peer counselling, resources, family support, and community outreach.

Conclusions There remains a need for an evidence-based approach to consistently define stability criteria for KMC to improve care. We found that KMC for unstable neonates weighing ≤2000g was feasible and acceptable at Jinja Hospital in Uganda. Randomised controlled trials are needed to demonstrate the effect of KMC on survival among unstable neonates in low-resource settings.

Each year, 15 million babies are born preterm (<37 completed weeks gestation) and 1 million deaths occur as a direct result of complications of preterm birth [1-3]. Sub-Saharan Africa and South Asia account for three-quarters of the 2.7 million neonatal deaths that occur annually, and preterm birth is the leading cause of these deaths [4]. Progress in preventing preterm birth has been limited, but major reductions in mortality could be achieved by improving care in low-resource settings [1,3,5,6]. In such settings, 50% of neonates born at 32 to 34 weeks gestation, a time when nearly all should survive, die because newborn special care is not available [3,7]. Kangaroo mother care (KMC) consists of early, continuous skin-to-skin contact (SSC), usually with the infant's mother; improved breastfeeding; and supportive care for neonates [8,9]. The most recent Cochrane review and a meta-analysis demonstrated that KMC among *stable* neonates ≤2000g is associated with decreased mortality (relative risk (RR) 0.60-0.64) [10,11], sepsis (RR 0.35-0.53) [10,11], hypothermia (RR 0.22-0.28) [10,11], and length of stay (LOS, mean difference -1.61 days) [10] compared to conventional care. WHO guidelines recommend KMC for "routine care of newborns weighing ≤2000 grams (g)… initiated as soon as newborns are clinically *stable*" [12].

However, most neonatal deaths occur in clinically *unstable* neonates within 48 hours of birth in settings without intensive care [3,7]. The only randomised controlled trial (RCT) of KMC in unstable neonates with mortality outcomes was conducted in Ethiopia (123 neonates ≤2000g) and reported major mortality impact (RR 0.57) [13]. Notably, this trial excluded >50% of eligible neonates, did not utilise allocation concealment, and had an apparent imbalance in gestational age and birthweight between groups (favouring KMC) at baseline [13,14]. Among 17 RCTs (14 enrolled only clinically stable neonates) comparing KMC with conventional care in low birthweight (LBW, <2500g) neonates aged <15 days, there was significant variability in how clinical stability was defined. Six defined this based on therapies [15-20], five on 'hemodynamic stability' [13,21-24], and three on specific vital sign parameters [25-27], while three provided no definition at all [28-30]. Hence codifying stability criteria for KMC is critical. A recent WHO guideline for care of preterm neonates highlighted the evidence gaps regarding KMC effect on mortality in *unstable* neonates. These included absence of criteria to identify which neonates are *stable enough* to safely receive KMC; the optimal time for initiation; and the duration required to reduce mortality [12].

Compared to other regions of the world, sub-Saharan Africa has experienced slow progress towards reducing neonatal mortality, particularly mortality due to preterm birth [2]. This is likely due to higher preterm prevalence and lower access to care [3,7], and shortages in health workers [31,32]. Further, many interventions are introduced to low-resource settings without adequate evidence of their effectiveness in such settings [3,31]. Incubators, the standard mode of thermal support for small and preterm neonates, are often unavailable or fail to function due to resource-related difficulties such as inconsistent electricity supply or access to replacement parts. Further, they require regular disinfection; however, this is often not done in resource-constrained settings [33]. Other potential issues include risk of cross-infection from other neonates when incubators are shared, and cost [34-36].

In Uganda alone, an estimated 45 000 newborn deaths occur annually, a quarter of which are due to complications of prematurity [37]. As a result, "national attention for maternal and child health has been clear and authorised from the highest levels" [38]. In 2006, the Ugandan government established a Newborn Steering Committee, which advised immediate action to increase the scale-up of KMC in facilities [38].

The purpose of this study was to explore the feasibility and acceptability of KMC for clinically unstable neonates weighing ≤2000g at Jinja Regional Referral Hospital in Uganda. Specifically, we aimed to:

1) determine the proportion of admitted neonates meeting proposed clinical instability criteria,
2) assess the feasibility of monitoring and providing interventions to unstable neonates ≤2000g in the KMC position, and
3) evaluate the acceptability of KMC for unstable neonates ≤2000g to parents and healthcare providers.

METHODS

Study setting

This study was conducted at Jinja Regional Referral Hospital, a facility in southeastern Uganda with a catchment area of 4 million. Jinja Hospital has ~6500 deliveries annually [39], and preterm birth is common. Sick and preterm/LBW neonates are cared for in the newborn unit, which admits approximately 1200 neonates annually. This unit is distinct from the postpartum ward, where healthy newborns receive

care. KMC is employed for neonates deemed *stable* by newborn unit staff. Mothers participate in the care of their babies by providing KMC, feeding (breastfeeding and nasogastric/cup feeds), and checking temperature. The standard mode of thermal support for unstable neonates is incubators, frequently with several neonates sharing an incubator.

Study design

This was a mixed-methods study consisting of three parts: an admissions audit, a feasibility sub-study, and an acceptability sub-study.

1) Admissions audit

Clinical instability was defined *a priori* as need for ≥2 medical therapies (oxygen, continuous positive airway pressure (CPAP), intravenous (IV) fluids, IV antibiotics, aminophylline, phenobarbital, or phototherapy) during the first 48 hours after birth. The audit aimed to determine the percentage of admitted neonates meeting the proposed criteria. A study coordinator and research assistant were trained on audit objectives and procedures. The target sample size was 250 neonates, based on the suggestion of Sackett et al [40] that 10 charts per variable are needed to obtain accurate and clinically useful results in a retrospective audit. Records were randomly selected across the 12-month audit period (June 2015 to May 2016). We retrospectively recorded data from the medical charts of neonates who were born at Jinja Hospital and admitted to the newborn unit within 48 hours of birth. The research assistant recorded birthweight, date and time of birth and admission, and treatments administered during the first 48 hours of admission. We excluded charts that were not satisfactorily complete, defined as including both birthweight and medical therapies administered, and those with birthweight >2000g from the analysis. To ensure data quality, the study coordinator randomly selected 10% of neonatal charts included in the audit, and double-entered data from those charts into data collection forms. We calculated the frequency and percentage of medical therapies received during the first 48 hours with 95% confidence intervals (CI), and the percentage of neonates meeting the proposed therapy-based instability criteria in that period.

2) Feasibility sub-study

Using instability criteria defined in the audit, we sought to demonstrate the feasibility of monitoring and providing clinical care and interventions (such as oxygen, IV fluids) to unstable neonates in the KMC position. The research team (paediatrician, nurse, study coordinator) and newborn unit nurses had training on the study objectives and procedures. Between July and December 2016, we enrolled a purposive sample of 10 neonates meeting the following eligibility criteria: 1) live-born at Jinja Hospital; 2) birthweight ≥700g and ≤2000g; 3) singleton; 4) chronological age <48 hours; 5) mother able and willing to participate in KMC; 6) infant unstable (defined as in the audit) at the time of enrolment, and followed them until discharge (up to a maximum of 14 days). We selected a small sample size due to the exploratory nature of the intervention and the inherent clinical risks in this vulnerable population. A KMC overview handout was provided and the study nurse counselled mothers during the consent process and throughout the study to provide KMC as close to continuously as possible with a goal of 18 hours per day. For purposes of this study, we defined a KMC episode as beginning when skin-to-skin contact (SSC) commenced and ending when SSC stopped. For interruptions due to mothers carrying out activities like bathing, a family member was encouraged to take over KMC. If none were available, the baby was placed in an incubator until the mother returned. Neonates were managed according to unit guidelines. The study paediatrician oversaw clinical decisions about enrolled neonates. All neonates received continuous monitoring of oxygen saturation (SpO_2) and heart rate (HR) using Masimo Rad-8 pulse oximeters. Monitoring was commenced at the time of KMC initiation and was continued throughout enrolment. To avoid interruption of KMC, a Bilisoft® phototherapy blanket (GE Healthcare, Chicago, IL, USA) was utilised to treat jaundice. The study nurse and unit nurses completed a data collection form, which recorded date and time of birth and admission, gestational age, birthweight, admission and discharge diagnoses, treatments administered, timing and duration of KMC episodes, date of breastfeeding initiation, LOS, and discharge disposition. Gestational age was calculated by last menstrual period (LMP). When LMP was unavailable, the study nurse conducted a Ballard examination [41]. We calculated the median duration of KMC per episode (minutes) and per day (hours) with interquartile ranges (IQR), and the mean number of concurrent medical interventions delivered per day with standard deviation (SD). Statistical analyses for the admissions audit and feasibility study were carried out using Stata 13 (StataCorp LP, College Station, TX, USA).

3) Acceptability sub-study

We assessed the acceptability of KMC for unstable neonates ≤2000g to parents and providers at Jinja Hospital. The sub-study utilised qualitative research methodology through semi-structured interviews with

20 key stakeholders. In qualitative research, the correct sample size is one that satisfactorily answers the research question [42]. Purposive sampling was utilised to select 10 parents of singleton neonates that were alive and hospitalised in the newborn unit at the time of the interview. All 10 newborn unit providers were included. Interviews took place between May and July 2016. Two interview guides were developed in English – one for parents and one for providers. The guide for parents was translated from English to Lusoga, the local dialect, and translated back to English to ensure accuracy and equivalence [43]. Interviews with parents were conducted in the language with which they were more comfortable. Interviews with providers were conducted in English. The interview guide employed open-ended questions about a broad range of potential factors while allowing the interviewer to ask additional questions on emerging themes. One female interviewer conducted the interviews in a private setting in the language of the participant's choice. Data validity was supported by the fact that the interviewer was a local woman who spoke the local language. The interviewer was familiar with techniques of qualitative research and had previous experience interviewing parents in a hospital setting. The protocol and interview guide were discussed in detail with the interviewer to ensure she understood the study objectives. Pilot interviews were conducted to identify and revise unclear interview questions and provide additional training on areas of weakness. Consent was requested to audiotape the interview. Interviews were held in a private room to provide confidentiality.

Thematic analysis

Interview data were transcribed and, where necessary, translated to English. The interviewer performed transcription with the assistance of an experienced Ugandan transcriptionist based at Makerere University. To improve quality control, a sample of early transcripts was compared to the audiotaped interviews to detect transcription errors and correct them. Data were analysed using the thematic content approach [44,45], which consisted of four steps: 1) familiarisation; 2) identifying codes and themes; 3) developing a coding scheme and applying it to the data; and 4) organising codes and themes. The principal investigator (PI) and interviewer read all transcripts and developed the preliminary coding scheme together. Two interviews were double coded by the PI and the interviewer, and any discrepancies were discussed and resolved to develop the final coding framework. The PI coded the remaining interviews. New themes that emerged outside the coding framework were also included in the analysis [46,47].

Ethical issues

All participants in the feasibility study received standard care available in the newborn unit at Jinja Hospital, including oxygen, CPAP, IV fluids, antibiotics, phototherapy, nasogastric feeds, and anti-convulsant and other medications as clinically indicated and available. Mechanical ventilation was not available. Following a full explanation about the study by the trained nurse (feasibility study) or interviewer (acceptability study) who spoke the local language, written informed consent was obtained from a parent/guardian (feasibility study) or the participant (acceptability study). Ethics Committee approvals were obtained from Makerere University, the Uganda National Council for Science and Technology, the London School of Hygiene and Tropical Medicine (LSHTM), and the University of California, San Francisco (UCSF).

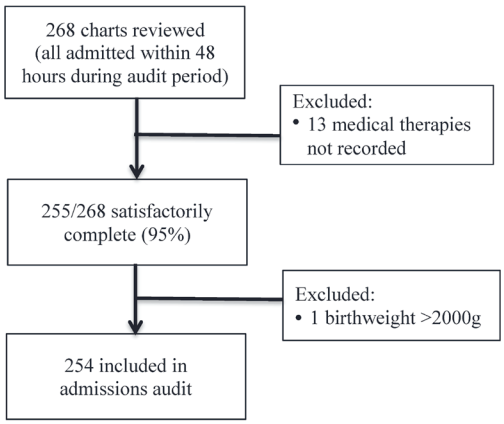

Figure 1. Flowchart showing inclusions and exclusions for admissions audit.

RESULTS

1) Admissions audit

A total of 268 charts were reviewed, among which 255 were satisfactorily complete and 254 met birthweight criteria (**Figure 1**).

Among the 254 included neonates, the mean birthweight was 1477g (SD 318g, range 500-2000g) and 139 (60%) were female. **Table 1** shows the frequency and percentage of all neonates, very low birthweight (VLBW, 1001-1500g) neonates, and extremely low birthweight (ELBW, 500-1000g) neonates with 95% CI by the number of medical therapies received during the first 48 hours after birth. Among all enrolled neonates, 226 (89%, 95% CI: 84.5-92.5) met the proposed instability criteria (≥2 medical therapies). Similarly, 99 (90%, 95% CI: 82.8-94.9) of VLBW neonates and 26 (90%, 95% CI: 72.6-97.8) of ELBW neonates met criteria for instability (**Table 1**).

Table 1. Number of medical therapies received among neonates in admissions audit (N = 254)

Number of medical therapies received*	Frequency (%) of all neonates, N = 254	95% CI	Frequency (%) of VLBW neonates, N = 110	95% CI	Frequency (%) of ELBW neonates, N = 29	95% CI
0 to 1	29 (11.4)	7.8-16.0	11 (10.0)	5.1-17.2	3 (10.3)	2.2-27.4
2	73 (28.7)	23.3-34.7	32 (29.1)	20.8-38.5	4 (13.8)	3.9-31.7
3	105 (41.3)	35.2-47.7	47 (42.7)	33.3-52.5	19 (65.5)	45.7-82.1
4 to 5	47 (18.5)	13.9-23.8	20 (18.2)	11.5-26.7	3 (10.3)	2.2-27.4

CI – confidence interval, VLBW – very low birth weight, ELBW – extremely low birth weight
*Oxygen, CPAP, IV fluids, IV antibiotics, aminophylline, phenobarbital, phototherapy.

Table 2. Feasibility study participant characteristics (N = 10)

Participant characteristics	Median (IQR)	Range
Birthweight (g)	1310 (820-1600)	700-1800
Gestational age (weeks)	28 (26-31)	26-35
Age at enrolment (hours)	25.3 (4.8-43.9)	1.7-47.1
LOS (days)	10 (9-14)	3-40
	Number	Percent
Female	7	70
Discharged	8	80
Died	2	20

IQR – interquartile range, LOS – length of stay

The instability criteria were easily implementable, leading to clear and timely identification of a substantial proportion of admitted neonates as unstable.

2) Feasibility sub-study

Table 2 shows the participant characteristics. Among the 10 neonates enrolled, median birthweight was 1310g, median gestational age was 28 weeks, median age at enrolment was 25.3 hours, and median LOS was 10 days. Eight neonates were discharged to home, all of whom were breastfeeding (3 with supplemental expressed breastmilk) at the time of discharge. Two neonates died during the study period; both were extremely premature (26-27 weeks) and extremely low birthweight (700-750g).

Amongst the 10 participants, we observed 315 KMC episodes over 102 person-days. The median age at KMC initiation was 30.3 hours (IQR: 19.6-95.2 hours). The provider was the mother in 298 (94.6%), the father in 2 (0.6%), and another family member in 15 (4.8%). Amongst the 8 participants that breastfed during the first 14 days of admission, the median age at breastfeeding initiation was 4.5 days (IQR: 2.0-7.5 days). The mean number of concurrent medical interventions was relatively constant across the first 14 days of admission, ranging from 3.7 to 4.1 interventions per day (Table 3). The median duration of individual KMC episodes was stable across this time period, ranging from 115 to 134 minutes. The median daily duration of KMC ranged from 4.5 hours (day 3) to 9.7 hours (day 13) with a slight upward trend over time (Figure 2). Two neonates received the target duration of 18 hours on day 1 (18.1 and 21.6 hours) and one neonate received the target duration on day 5 (18.3 hours). The number of concurrent medical interventions an infant was receiving did not affect the daily duration of KMC (Figure 3).

Table 3. Concurrent interventions and KMC duration by study day (N = 10)

Study day	Mean (SD) number of interventions	Range number of interventions	Mean (range) number of KMC episodes	Median (IQR) duration of KMC episodes (minutes)	Median (IQR) daily duration of KMC (hours)
1 (n = 10)	4.0 (0.67)	3-5	2.4 (0-5)	120 (108-146.5)	5.1 (3.0-8.6)
2 (n = 10)	3.9 (0.88)	2-5	2.6 (0-5)	115 (65-140)	5.1 (0-8.4)
3 (n = 10)	4.1 (0.99)	2-5	2.0 (0-5)	120 (65-168)	4.5 (1.0-7.0)
4 (n = 9)	4.0 (1.0)	2-5	3.3 (0-4)	131 (120-196)	8.5 (6.7-9.5)
5 (n = 9)	4.0 (1.0)	2-5	3.3 (2-5)	120 (60-148)	7.4 (5.0-8.3)
6 (n = 9)	3.9 (1.05)	2-5	3.0 (0-5)	130 (100-156)	6.1 (5.0-7.3)
7 (n = 9)	3.7 (1.22)	1-5	3.4 (0-6)	120 (108-202)	8.1 (6.0-11.9)
8 (n = 9)	3.7 (1.41)	1-5	3.0 (0-4)	120 (108-146.5)	6.7 (4.4-10.3)
9 (n = 8)	3.5 (1.41)	1-5	3.1 (1-6)	120 (88-138)	6.3 (2.4-9.6)
10 (n = 4)	4.0 (0.82)	3-5	4.0 (2-5)	120 (75-146)	8.3 (6.0-9.8)
11 (n = 4)	4.0 (0.82)	3-5	4.0 (3-5)	129 (92-162.5)	9.3 (7.2-10.1)
12 (n = 4)	3.8 (0.96)	3-5	4.0 (3-5)	134 (80-155)	7.5 (6.5-10.8)
13 (n = 4)	3.8 (0.96)	3-5	4.5 (3-6)	132 (90-160)	9.7 (8.4-11.4)
14 (n = 4)	3.8 (0.96)	3-5	3.0 (2-4)	120 (84-163)	5.6 (4.1-8.4)

KMC – kangaroo mother care, SD – standard deviation, IQR – interquartile range

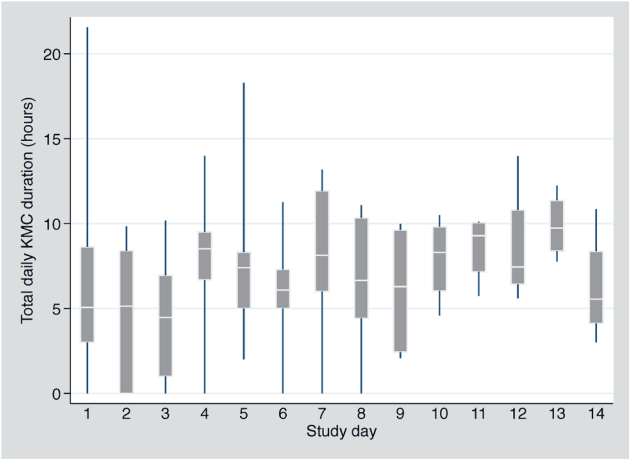

Figure 2. Daily kangaroo mother care (KMC) duration (median, IQR, 5th-95th percentiles) by study day (N = 10).

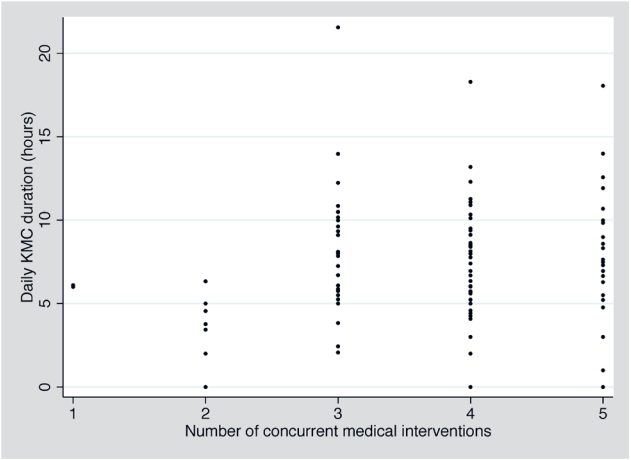

Figure 3. Daily kangaroo mother care (KMC) duration by number of concurrent medical interventions (N = 10).

Table 4. Acceptability study participant characteristics (N = 20)

Parent characteristics, n = 10		Provider characteristics, n = 10	
Age (median, range)	27 (22-35)	Age (median, range)	48.5 (29-55)
Demographic characteristics		**Role in Newborn Unit**	
Mother	8 (80%)	Paediatrician	2 (20%)
Married	7 (88%)	Charge nurse/nurse officer	2 (20%)
Resides in rural area	5 (63%)	Midwife	6 (60%)
Father	2 (20%)	Educational level	
Married	2 (100%)	Diploma	6 (60%)
Resides in urban area	2 (100%)	Certificate	2 (20%)
Educational level		Master's degree	2 (20%)
Primary	3 (30%)		
Secondary	5 (50%)		
College	2 (20%)		

3) Acceptability sub-study

We enrolled 20 key stakeholders (10 parents, 10 providers). Table 4 shows the participant characteristics.

We use the main themes emerging from the data to structure the presentation of material from the interviews, with themes broadly classified as facilitators or barriers, as below.

Facilitators

General knowledge about KMC and its benefits

All parents and providers knew KMC is a method to provide warmth to preterm babies through SSC, usually with the mother.

> *"It's a traditional or African way of keeping a baby warm; it is usually for babies that are born preterm. You put the baby on the chest of the mothers. It creates love between the mum and child."* (Father, age 28)

While most parents reported that the mother is the KMC provider, several health care providers stated that other family members could also deliver KMC. Parents and providers agreed that KMC promotes breastfeeding and infant bonding. One mother also said KMC promotes connection between parents.

> *"As a KMC father myself, I felt that there was a lot of bonding between myself and my daughter. She is 9 years old now. I feel like I have bonded with her more than my other children. Each time I meet someone, I proudly tell them, 'This is my daughter.' When people say, 'so what,' I tell them that she was 900 grams and look at how she has grown."* (Paediatrician, age 52)

Half of providers mentioned that KMC promotes immunity and overall health in unstable preterm and LBW neonates. One provider described how they encourage mothers to practice KMC to help stabilise neonates when oxygen is unavailable.

> *"When the power has gone, we encourage mothers to do it to help stabilize the breathing when the oxygen is off."* (Midwife, age 29)

Improved monitoring of unstable neonates

The majority of providers felt that KMC leads to improved monitoring of unstable neonates, compared to incubator care.

> *"While the baby is on KMC, the monitoring is better because the mum is always there. However, if the baby is an incubator, the nurse may not be able to check on the baby frequently because of the limited human resources available."* (Paediatrician, age 55)

The majority of parents also felt that KMC leads to improved infant monitoring. Three mothers and one father additionally described how practicing KMC gave them a sense of responsibility in caring for their babies.

> *"Because I want my baby to be looked after properly, I start to become responsible for my child and I find myself looking to see what's wrong and letting the doctor know."* (Mother, age 27)

Almost half of providers stated that improved availability of monitoring devices would help facilitate KMC provision amongst unstable neonates.

> *"If it's there, it would work. Something preferably with lights that's easier for mums to remember."* (Charge nurse, age 50)

Provision of medical interventions in the KMC position

Seventy-five percent of parents and providers felt that medical therapies (eg, oxygen, IV fluids) can be provided to neonates while in the KMC position.

> *"I don't think there are any concerns because the baby can face either side of the mother's chest while they are receiving oxygen and IV fluids."* (Midwife, age 51)

KMC initiation

The majority of parents and providers felt KMC could be used in the first 48 hours after birth.

> *"I think it's a good idea because that skin-to-skin contact will stabilise the baby's temperature faster than an incubator."* (Midwife, age 51)

Staff and peer counselling

All providers and the majority of parents agreed that staff counselling is essential to promote KMC amongst unstable neonates. Three providers and three parents stated that peer counselling is a valuable approach to promote KMC in the hospital. One provider suggested a follow-up club where mothers could talk to each other about KMC and preterm care.

> *"Peer counselling is key because another mum in the ward can share her experience; we have found that peer counselling is more important and effective than counselling from a doctor or nurse."* (Paediatrician, age 55)

> *"We like the follow-up clinic on Friday because it gives the mums a chance to talk amongst each other. You will often hear them ask "I put my child like this, is this the right way?" They also compare and contrast. We also encourage mothers to teach each other on the proper way to do it."* (Paediatrician, age 52)

Family support and meal provision

Almost half of providers discussed the importance of family support, with two specifically commenting on the role of the mother in law in influencing KMC practice in facilities.

> *"The management of the baby is a combination of the mum, the nurses and the doctors, but also the relatives. The mothers need support from the relatives to survive in the hospital."* (Charge nurse, age 50)

One provider and one mother mentioned that provision of meals in the newborn unit would be helpful to mothers who lack family support and money.

Concerns related to incubators

Half of parents expressed concerns that incubators were unsafe, some stating they cause brain damage.

> *"Sometimes I think an incubator can harm the baby's brain. There is no love, just heat, in the incubator."* (Mother, age 22)

One provider and one mother mentioned the shortage of incubators in the newborn unit.

> *"The incubators are not enough because sometimes your baby could be there and then the doctor comes in with a much sicker baby and they remove yours and the cycle continues like that until your baby never goes back to the incubator."* (Mother, age 32)

Cost savings and sustainability of KMC

Three providers stated that KMC is less costly than incubator care. One mother mentioned the sustainability of KMC and one provider discussed the applicability of KMC across different income and education levels.

> *"It is appropriate in every household regardless of someone's level of civilization. We believe it has bigger advantages which is less cost and sophistication and less risks in terms of temperature and it is sustainable."* (Paediatrician, age 52)

Community outreach and education

Three providers and two parents felt that provision of KMC education in antenatal clinics and elsewhere in local communities would help promote KMC practice amongst hospitalised neonates. One provider suggested that such outreach could involve mothers of former preterm neonates teaching members of their local community about KMC.

> *"Some mums don't have sheets and hats to do KMC… they come unprepared. We provide the hats, but the sheets we don't have anymore. Some counselling and training on KMC needs to be done in the antenatal ward to prepare mums."* (Nursing officer, age 50)

> *"I believe KMC training should start as far as the rural areas; there are some health workers there I'm sure don't know about it. It would be beneficial; this training would then extend to health centre-3s* [lowest level facility in Uganda at which deliveries are allowable] *and go to antenatal care as well."* (Father, age 28)

Barriers

Stigma and guilt related to prematurity

Several providers mentioned that stigma and guilt about having a preterm infant are common in the local communities.

> *"The mothers that are getting preterm babies for the first time are reluctant to help because they don't believe that these babies can survive."* (Charge Nurse, age 50)

> *"Acceptability of this baby is an issue; some mums accept their babies while others, especially those that have had normal births in the past, are torn up about it."* (Paediatrician, age 55)

Several mothers described personal observations about the high risk of death in preterm babies.

> *"I have seen some babies die, especially those that range between 5 and 5.5 months. These babies are at a higher risk of dying than those that are 6 or even 7 months. They usually pass away."* (Mother, age 32)

Concerns related to infant monitoring

Providers agreed that monitoring unstable neonates in the KMC position can be challenging due to staff shortages and/or lack of monitoring devices.

> *"I worry sometimes because these mothers may not observe the baby; in some situations, the baby may fall inside without the mother noticing… we have to pay extra attention to these mums in the event they aren't monitoring their baby."* (Midwife, age 51)

One mother expressed concern that her baby might be monitored less closely, but agreed that KMC allows mothers to learn more about the care of preterm neonates.

> *"I'm very worried that doing KMC would not allow my baby to be monitored as much because the baby can change colour at any time and you aren't sure what's wrong. Sometimes as mothers, we don't know the difference in colour change. However, it also allows the mother to learn more about her baby and update the doctor or nurse."* (Mother, age 32)

Concerns related to pain and dislodgement of tubing

A few mothers expressed concern that doing KMC while receiving oxygen or IV fluids could be painful for the baby or could lead to accidental dislodgement of tubing.

> *"I want to be close to him and I feel like those tubes would hurt him as we are doing KMC."* (Mother, age 26)

One mother discussed the difficulties of KMC provision following a caesarean delivery.

> *"I had a caesarean section and I couldn't move properly or even hold a baby for at least 3 or even 4 days so I wasn't able to do KMC immediately."* (Mother, age 30)

Lack of family support, finances, and time away from work

One mother stated that lack of family support and lack of money for mothers to buy food are common in the newborn unit. A father discussed difficulties with KMC related to cost and increased time away from work.

> *"I was supposed to work but I had to get the day off and come here so that they could be discharged from the hospital because it's becoming very expensive. The more time we are here, the more money I have to spend."* (Father, age 25)

Lack of beds, space, and privacy

All providers and 80% of parents felt that lack of beds and space in the newborn unit was a barrier to KMC practice. Twenty percent of providers and 80% of parents, including both fathers, perceived lack of privacy to be an issue.

> *"You are a man and they are making you take off your shirt; I know men are shy. If there was a place with less people and you are free, that would be good."* (Father, age 25)

Lack of KMC education

Half of parents felt that lack of education was a barrier to KMC provision in facilities.

> *"Sometimes there are students here and they don't tell us about KMC and then by the time we are learning it has been three days after!"* (Mother, age 23)

Lack of motivation amongst parents

Three providers described how it can be difficult to motivate mothers to devote sufficient time to KMC.

> *"Some of these mothers don't find it realistic to sit with their babies for that period of time and ultimately don't enjoy it. They want it to be quick."* (Midwife, age 29)

DISCUSSION

To our knowledge, this is the first study to evaluate the incidence of clinical instability, as well as the feasibility and acceptability of KMC in this vulnerable population.

Instability criteria

We found that the majority of neonates weighing ≤2000g admitted within 48 hours of birth in this regional hospital met our criteria for clinical instability. Based on a review of currently available evidence, we defined instability by the need for ≥2 medical therapies. For public health impact, it was crucial to select criteria that would permit inclusion of the majority of vulnerable neonates, who face the highest risk of mortality, while still ensuring safety. Importantly, these therapy-based criteria identified 89% of all LBW neonates and 90% of VLBW and ELBW neonates as unstable within 48 hours of birth. We hypothesised that these criteria would identify all ELBW neonates as unstable; however, it is possible that some administered therapies were not properly recorded in medical charts. There remains a need for an evidence-based approach to consistently define stability criteria in order to improve clinical care and facilitate research in this population [12,48].

Feasibility

We found that it is feasible to monitor and provide medical interventions to unstable neonates in the KMC position. Underlining the vulnerability of these preterm neonates, two of the 10 enrolled neonates died during the 14-day enrolment period. Both were extremely premature and extremely low birthweight, thus at very high risk of death, particularly in a low-resource setting given the lack of ventilatory support and other intensive care usually required for survival at this gestational age. The median age at enrolment was 25.3 hours, and neonates received a median duration of KMC ranging from 4.5 to 9.7 hours per day with a slight upward trend over time. This is comparable to findings from several RCTs, which reported me-

dian daily durations of ≥4 to 10 hours with mean/median age at enrolment ranging from <1 to 4.7 days [15,21-24,28]. Notably, despite nurse counselling, few neonates achieved the target KMC duration of 18 hours per day (two on day 1 and one on day 3). Three RCTs evaluating continuous KMC reported durations of ≥20 hours per day with mean/median age at enrolment of 4 days [17], 10 days [16], and 13 days [30]. Studies have shown that continuous KMC can be difficult to achieve as mothers may find it overwhelming, and clinicians and administrators may be unaware of the need for near-continuous provision [49]. In this study, the number of concurrent medical therapies an infant was receiving did not affect the daily duration of KMC. The median duration of individual KMC episodes was approximately 2 hours across the study period. Experts have suggested that a minimum episode duration of 2 hours is important [9] because it provides the stimulation needed to increase milk volume and facilitate let-down; facilitates the infant spontaneously awakening, self-regulating feeding, and completing a sleep cycle [50,51]; and reduces the number of transfers into and out of the KMC position [52].

Acceptability

We found that stigma and guilt related to having a preterm baby is common in local communities in southeastern Uganda. Another study in this region found that most of the mothers interviewed believed that preterm babies could survive if treated properly. However, that study also found that some mothers wished their preterm neonates had never been born [53]. Other studies have also reported stigma, fear, shame, or guilt in association with having a preterm infant [54–56]. All participants knew that KMC provides warmth to small or preterm neonates. Participants were also aware that KMC promotes breastfeeding, stimulates breathing, and promotes infant bonding. Other studies in low-resource settings have also reported knowledge of these benefits [56-58]. In particular, the effect of KMC on parent-infant bonding has been widely reported [9,59-63]. In this study, most parents stated that the mother is the KMC provider. In another Ugandan study, most men interviewed felt that women were the sole KMC providers [53]. The majority of parents and providers found use of KMC among neonates who are receiving concurrent medical therapies in the first 48 hours after birth acceptable. A few mothers expressed concern that KMC might cause pain or displace IV/oxygen tubing, worries that have also been seen in neonatal units in high- and upper middle-income settings [64-67]. The majority of parents and providers felt that KMC leads to improved infant monitoring. Other studies have also found that parents feel more responsible for the health of their neonates when providing KMC [9,56].

Our study found that lack of beds/space, privacy issues, insufficient staff and devices for monitoring, inadequate KMC education, and difficulties motivating mothers to devote time were the most common barriers to KMC practice. Other studies have also reported that lack of space, privacy, and KMC resources hindered KMC practice [54,68-72]. A study in Malawi found that lack of recreational activities was an obstacle [57]. Parents and providers suggested that KMC practice could be improved through staff and peer counselling, more beds/space, improved availability of monitoring devices, family support, and community outreach. Several studies have noted the importance of staff training and counselling on KMC [73,74], and a related RCT demonstrated the efficacy of peer counselling in promoting breastfeeding amongst admitted preterm neonates [75]. Other studies have noted the importance of family support, particularly from the father and mother in law [49,57,63,76], and other social support, such as from peers and nurses, in promoting KMC [49,77,78]. In support of the recommendation for community outreach, a study found that zero of 16 health centres in two districts of eastern Uganda promoted KMC practice. Further, local community members had minimal knowledge about KMC [53].

Limitations

This study has limitations. Audit findings are limited especially by incomplete records, a common issue in low-resource contexts. To address the latter, we excluded charts that were not satisfactorily complete, which were defined as including both birthweight and medical therapies administered. Our feasibility findings are based on a sample of only 10 neonates, which is too small to draw firm conclusions. Importantly, however, we continuously observed clinical care and KMC practice from the time of enrolment to discharge, up to a maximum of 14 days. In a recent systematic review, only 12% of included studies reported the duration of KMC [79]. For the acceptability sub-study, we interviewed 10 parents (8 mothers and 2 fathers) and 10 providers who had experienced a preterm birth or cared for preterm neonates, respectively. Participants were assured that their responses were confidential in nature, and would not affect the care of their infant in any way; however, social desirability bias may have influenced the responses of some parents.

CONCLUSIONS

This study demonstrates that KMC for neonates meeting criteria for clinical instability, defined as the need for ≥2 medical therapies in the first 48 hours, was feasible in a small sample of neonates weighing ≤2000g and acceptable to parents and providers at Jinja Hospital in Uganda. To improve clinical care and facilitate research, there remains a need for an evidence-based approach to consistently define stability criteria for KMC. Further, RCTs are crucial to examine the effect of KMC on survival in this vulnerable population. Such evidence would have broad applicability, especially in low-resource settings where most neonatal deaths occur.

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7. Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa (OMWaNA): protocol for a randomised controlled trial to examine mortality impact in Uganda (Paper D)

7.1. Scope of this chapter

Chapter 7 presents the fourth research paper entitled, "Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa (OMWaNA): protocol for a randomised controlled trial to examine mortality impact in Uganda." This paper describes the protocol for the OMWaNA trial and provides an overview of the accompanying economic and process evaluations. The primary aim of the trial is to determine the effect of KMC initiated before stabilisation on mortality within 7 days relative to standard care amongst neonates ≤2000g at four government hospitals in Uganda (Entebbe, Jinja, and Masaka Regional Referral Hospitals and Iganga District Hospital). The OMWaNA trial is funded by the Joint Global Health Trials scheme of the Department of Health and Social Care, the Department for International Development, the Medical Research Council, and the Wellcome Trust.

This work was published in *Trials* as an open access article in January 2020. See Appendix A.7.1 for the copyright.

The OMWaNA Inception Meeting was held in February 2019 (Figure 7-1) and the Trial Implementation Meeting was held in August 2019 (Figure 7-2). Following completion of renovations (Figure 7-3) and a pilot phase, the trial commenced recruitment in January 2020.

Figure 7-1. OMWaNA Inception Meeting in Entebbe with hospital directors, paediatricians, and nurse matrons from the four Ugandan trial sites, February 2019

Figure 7-2. Members of the OMWaNA team participating in the 'KMC Challenge' at the Trial Implementation Meeting in Entebbe, August 2019

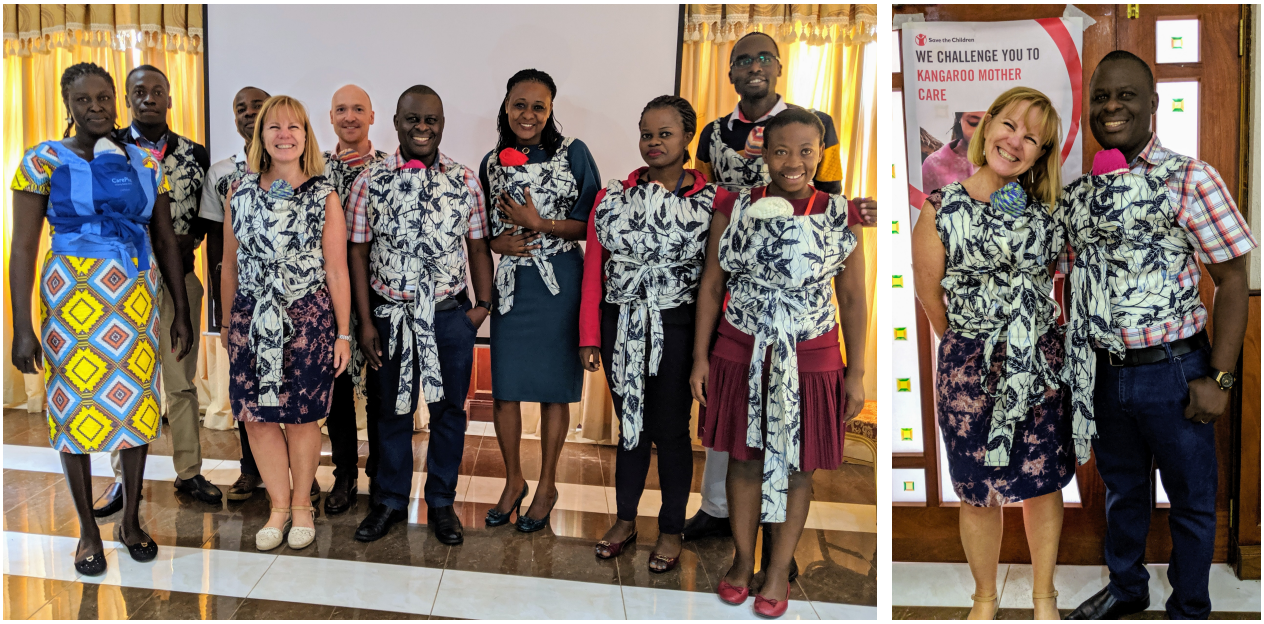

Figure 7-3. OMWaNA team members and collaborators visiting the newly refurbished neonatal unit at Entebbe Regional Referral Hospital, August 2019

7.2. List of figures

7.3. List of tables

7.4. Citation

Medvedev MM, Tumukunde V, Mambule I, Tann CJ, Waiswa P, Canter RR, Hansen CH, Ekirapa-Kiracho E, Katumba K, Pitt C, Greco G, Brotherton H, Elbourne D, Seeley J, Nyirenda M, Allen E, Lawn JE. **Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa (OMWaNA): protocol for a randomised controlled trial to examine mortality impact in Uganda**. *Trials* 2020; 21:126. doi: 10.1186/s13063-019-4044-6.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	131393	**Title**	Dr
First Name(s)	Melissa Morgan		
Surname/Family Name	Medvedev		
Thesis Title	Informing the design of a trial of kangaroo mother care initiated before stabilisation amongst small and sick newborns in a sub-Saharan African context using mixed methods		
Primary Supervisor	Elizabeth Allen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Trials as: Medvedev MM, Tumukunde V, Mambule I, Tann C, Waiswa P, Canter RR, Hansen CH, Ekirapa-Kiracho E, Katumba K, Pitt C, Greco G, Brotherton H, Elbourne D, Seeley J, Nyirenda M, Allen E, Lawn JE. Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa (OMWaNA): protocol for a randomised controlled trial to examine mortality impact in Uganda. Trials. 2020; 21: 126. doi: 10.1186/s13063-019-4044-6.		
When was the work published?	31 January 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not applicable		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	With Prof Joy Lawn, I co-led design of the study and preparation of the Joint Global Health Trials funding application, with input from Drs Cally Tann and Peter Waiswa; Profs Elizabeth Allen and Diana Elbourne; and Ms Catherine Pitt. I drafted the trial protocol, with input from Profs Lawn, Allen, and Elbourne; Drs Tann, Waiswa, and Helen Brotherton; and Ms Ruth Canter. With Prof Lawn and Dr Tann, I co-designed the process and qualitative evaluations, with input from Drs Waiswa and Victor Tumukunde, and Profs Elbourne and Janet Seeley. I provided input on the design of the economic evaluation. I prepared trial case report forms and standard operating procedures with Drs Tumukunde, Ivan Mambule, and Tann, Ms Canter, and Mr Kenneth Katumba, with input from Profs Lawn, Allen, and Elbourne, and Drs Waiswa, Christian Hansen, Elizabeth Ekirapa-Kiracho, and Brotherton. I am a member of the team responsible for protocol implementation with Drs Tumukunde, Mambule, and Tann, Ms Canter, and Mr Katumba, with oversight by Profs Lawn, Allen, Elbourne, and Moffat Nyirenda; Drs Waiswa and Ekirapa-Kiracho; and Ms Pitt. I wrote the first draft of the manuscript and prepared all subsequent revisions with consideration of comments from co-authors. See Annex A.1. for full details.

SECTION E

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Date	3 February 2020

Supervisor Signature	Elizabeth Allen
Date	04/02/2020

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Trials

STUDY PROTOCOL Open Access

Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa (OMWaNA): protocol for a randomised controlled trial to examine mortality impact in Uganda

Melissa M. Medvedev[1,2,3*], Victor Tumukunde[4], Ivan Mambule[4], Cally J. Tann[1,3,4,5], Peter Waiswa[6,7], Ruth R. Canter[3], Christian H. Hansen[3,4], Elizabeth Ekirapa-Kiracho[6], Kenneth Katumba[4], Catherine Pitt[8], Giulia Greco[4,6,8], Helen Brotherton[1,3,9], Diana Elbourne[3], Janet Seeley[4,8], Moffat Nyirenda[3,4], Elizabeth Allen[3] and Joy E. Lawn[1,3]

Abstract

Background: There are 2.5 million neonatal deaths each year; the majority occur within 48 h of birth, before stabilisation. Evidence from 11 trials shows that kangaroo mother care (KMC) significantly reduces mortality in stabilised neonates; however, data on its effect among neonates before stabilisation are lacking. The OMWaNA trial aims to determine the effect of initiating KMC before stabilisation on mortality within seven days relative to standard care. Secondary objectives include exploring pathways for the intervention's effects and assessing incremental costs and cost-effectiveness between arms.

Methods: We will conduct a four-centre, open-label, individually randomised, superiority trial in Uganda with two parallel groups: an intervention arm allocated to receive KMC and a control arm receiving standard care. We will enrol 2188 neonates (1094 per arm) for whom the indication for KMC is 'uncertain', defined as receiving ≥ 1 therapy (e.g. oxygen). Admitted singleton, twin and triplet neonates (triplet if demise before admission of ≥ 1 baby) weighing ≥ 700–≤ 2000 g and aged ≥ 1–< 48 h are eligible. Treatment allocation is random in a 1:1 ratio between groups, stratified by weight and recruitment site. The primary outcome is mortality within seven days. Secondary outcomes include mortality within 28 days, hypothermia prevalence at 24 h, time from randomisation to stabilisation or death, admission duration, time from randomisation to exclusive breastmilk feeding, readmission frequency, daily weight gain, infant–caregiver attachment and women's wellbeing at 28 days. Primary analyses will be by intention-to-treat. Quantitative and qualitative data will be integrated in a process evaluation. Cost data will be collected and used in economic modelling.

(Continued on next page)

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(Continued from previous page)
Discussion: The OMWaNA trial aims to assess the effectiveness of KMC in reducing mortality among neonates before stabilisation, a vulnerable population for whom its benefits are uncertain. The trial will improve understanding of pathways underlying the intervention's effects and will be among the first to rigorously compare the incremental cost and cost-effectiveness of KMC relative to standard care. The findings are expected to have broad applicability to hospitals in sub-Saharan Africa and southern Asia, where three-quarters of global newborn deaths occur, as well as important policy and programme implications.

Trial registration: ClinicalTrials.gov, NCT02811432. Registered on 23 June 2016.

Keywords: Preterm, Low birthweight, Newborn, Kangaroo care, Skin-to-skin contact, Neonatal mortality, Randomised controlled trial, Pragmatic

Background

An estimated 2.5 million neonatal deaths occurred in 2018, accounting for nearly half of all deaths in children aged < 5 years [1]. Within the neonatal period, 36% of deaths occur on the day of birth and 73% occur in the first week [2]. Over 80% of neonatal deaths occur in low birthweight (LBW; weighing < 2500 g) babies, of which two-thirds are born preterm (≤ 37 weeks gestational age) [3]. Complications of prematurity are the leading cause of neonatal and under-5 mortality [1]. Approximately two-thirds of the 21 million LBW and 15 million preterm babies born each year are born in sub-Saharan Africa or southern Asia [4–6]. Together, these two regions are responsible for 78% of neonatal deaths [1]. With rates of preterm birth rising or stagnant across the globe [5, 6], finding ways to improve survival and reduce morbidity in preterm babies is a growing imperative.

Substantial progress could be achieved by improving facility-based care of small and sick babies in low- and middle-income countries (LMIC) [7, 8], Estimates suggest that available interventions could reduce prematurity-related mortality by 58% [9]. Kangaroo mother care (KMC) is an intervention consisting of early skin-to-skin contact, promotion of exclusive breastmilk feeding, early hospital discharge, and adequate support and close follow-up at home [10]. The latest Cochrane review (21 trials) and a meta-analysis (124 studies) demonstrated that KMC among *stable* neonates ≤ 2000 g is associated with decreased mortality [11, 12], sepsis [11, 12], hypothermia [11, 12], hypoglycaemia [12] and length of stay [11] compared to conventional care. WHO guidelines recommend KMC for 'routine care of newborns weighing ≤ 2000g… initiated as soon as newborns are clinically *stable*' [13]; however, there is significant variability in how stability has been defined in previous randomised controlled trials (RCT) of KMC [14].

The majority of neonatal deaths occur within 48 h of birth [2], and before stabilisation. The only RCT of KMC initiated before stabilisation with mortality outcomes was conducted in Ethiopia, enrolling 123 newborns weighing < 2000 g [15]. It reported a 43% reduction in mortality; however, 66% of deaths and the major difference between arms occurred within 12 h of birth [15, 16]. Further, this trial excluded > 50% of eligible neonates, did not utilise allocation concealment and had an apparent group imbalance at baseline (favouring KMC) [15], compromising robustness. Hence, the effect of initiating KMC before stabilisation remains an unaddressed research priority and a well-designed RCT, with clear criteria for stability, is warranted to examine mortality impact in non-intensive care settings [16, 17]. The OMWaNA trial aims to determine the effect of KMC initiated before stabilisation on mortality within 7 and 28 days relative to standard care at four hospitals in Uganda.

There are few published economic evaluations of KMC, and none conducted rigorously in low-resource settings from a societal perspective or with systematic equity assessment. Several studies in LMIC settings have found that KMC resulted in cost savings for the hospital or provider [18–21]; however, none has considered whether KMC may increase costs to households nor purposely evaluated KMC initiated before stabilisation. Evidence gaps remain with regards to estimation of the incremental cost, cost-effectiveness, budget impact and equity of KMC before stabilisation, particularly considering the household and societal perspectives. An economic evaluation embedded within the trial will compare the incremental cost and cost-effectiveness of KMC relative to standard care.

Rigorous studies examining causal pathways for the effects of KMC on neonatal health outcomes have not been conducted; thus, scientific understanding is limited. Potential underlying mechanisms may include improved thermal control [11, 12], enhanced cardiorespiratory stability [22, 23], increased breastmilk volume [24, 25], oxytocin-mediated attenuation of the stress response [26, 27] and thermally mediated reduction in the risk of intraventricular haemorrhage (IVH) [28]. The relevance of these hypothesised causal pathways in neonates for whom KMC is initiated before stabilisation is unclear, particularly IVH risk among very low birthweight

(VLBW; < 1500 g) newborns. Incubators, which are the standard alternative to KMC, may increase the risk of nosocomial infections, particularly in newborn units with ineffective cleaning standards or where incubators are shared [29, 30]. Thus, further research is warranted to improve scientific understanding of the physiological processes underlying the effect of KMC relative to standard care in this vulnerable population.

Methods/design

This manuscript has been prepared according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Additional file 1).

Objectives

The primary objective of the OMWaNA trial is to determine the effect of KMC initiated before stabilisation on mortality within seven days relative to standard care among neonates weighing ≤ 2000 g. Secondary objectives include:

1. Determining the effect of KMC initiated before stabilisation on other important clinical outcomes relative to standard care among neonates weighing ≤ 2000 g;
2. Estimating the incremental costs and cost-effectiveness of KMC initiated before stabilisation relative to standard care from the societal perspective;
3. Exploring hypothesised causal pathways for the clinical effects of KMC initiated before stabilisation relative to standard care among neonates weighing ≤ 2000 g;
4. Examining the barriers and facilitators to initiating KMC before stabilisation to inform uptake and sustainability in Uganda.

Study design

This is a four-centre, open-label, individually randomised, superiority trial with two parallel groups: an intervention arm allocated to receive KMC and a control arm allocated to receive standard care. Treatment allocation is random in a 1:1 ratio between groups.

Study setting

The host institution for the trial is the Medical Research Council/Uganda Virus Research Institute (MRC/UVRI) and London School of Hygiene & Tropical Medicine (LSHTM) Uganda Research Unit in Entebbe. The trial is being undertaken in collaboration with Makerere University and LSHTM. The trial is being conducted at four Ugandan government hospitals: Entebbe, Jinja and Masaka Regional Referral Hospitals and Iganga District Hospital (Fig. 1).

Uganda has a population of 42.9 million and is ranked 162/189 on the Human Development Index (2017) [31]. The population is predominately rural (76%) and the poverty incidence is 27% nationally [32]. Poverty rates vary considerably, with the highest rates occurring in rural areas where subsistence farming is the primary source of income. The Busoga sub-region, where Jinja and Iganga are located, has the third highest incidence of poverty in the country (42.1%), while the Wakiso sub-region, where Entebbe is located, has the second lowest (7.5%) [32].

In Uganda, the neonatal mortality rate is estimated at 19.9 per 1000 live births, with a resultant 32,296 deaths in 2018 [1]. Complications of prematurity are responsible for 27% of neonatal deaths [33], as compared to 35% globally [1]. An estimated 107,921 (7%) Ugandan babies were born preterm in 2014 [5].

Characteristics of the four trial hospitals are shown in Table 1. Each hospital has a neonatal special care unit, which accepts referrals from their respective region/district. The level of equipment in these government facilities differs, but all have: bag-mask resuscitation; incubators and/or overhead radiant heaters for thermal support; intravenous (IV) fluids, nasogastric tubes and syringes for feeding support; oxygen supply (concentrators or cylinders) and nasal prongs for respiratory support; IV and oral antibiotics; phototherapy for jaundice; aminophylline for prematurity-associated apnoea; and phenobarbital for seizures. Pulse oximetry and improvised bubble continuous positive airway pressure (CPAP) ventilation are available at some of the trial hospitals. Invasive ventilation and surfactant are unavailable at all sites. Standard care at the four sites involves provision of intermittent KMC to neonates weighing ≤ 2000 g once stable, in line with current WHO guidelines.

Study population

The trial will include admitted neonates weighing ≤ 2000 g for whom the indication for KMC is 'uncertain' according to WHO guidelines concerning clinical stability [10]. Eligibility criteria are listed below.

Inclusion criteria:

- Neonate admitted to trial hospital (inborn or outborn);
- Singleton, twin or triplet (if triplet pregnancy resulted in demise or stillbirth of ≥ 1 fetus);
- Birthweight ≥ 700 g and ≤ 2000 g;
- Chronological age ≥ 1 h and < 48 h at time of screening;
- Alive at time of recruitment;
- Parent/caregiver able and willing to provide KMC;
- Parent/caregiver willing to attend follow-up visit;
- Indication for KMC 'uncertain' according to WHO guideline concerning clinical stability: pragmatically defined as receiving ≥ 1 therapy: oxygen; CPAP; IV

Fig. 1 Map of Uganda showing location of the four OMWaNA trial hospitals. Source of map data: Google Maps©, 2019

fluids; therapeutic antibiotics (for suspected or confirmed infection); phenobarbital.

Exclusion criteria:

- Result of triplet or higher-order multifetal pregnancy (unless triplet pregnancy resulted in demise or stillbirth of ≥ 1 fetus);
- Indication for KMC 'certain' according to WHO guidelines: pragmatically defined as clinically well neonates receiving none of the above therapy-based criteria;
- Severely life-threatening instability defined as oxygen saturation (SpO_2) < 88% in oxygen and ≥ 1 of:
  - Respiratory rate < 20 or > 100 breaths/min;
  - Apnoea requiring bag-mask ventilation;
  - Heart rate (HR) < 100 or > 200 beats/min;
- Severe jaundice requiring immediate management;
- Active neonatal seizures;
- Major congenital malformation;
- Parent does not provide written informed consent to participate in trial.

Study procedures

The schedule of procedures for the OMWaNA trial is outlined in Fig. 2.

Figure 3 describes the flow of participants from the time of screening through follow-up at 28–30 days.

Screening

All admitted neonates weighing ≤ 2000 g at the four trial hospitals will be screened for eligibility by a study nurse or medical officer (Fig. 3a, 'Screening for eligibility'). Eligibility will be assessed as soon as possible after admission and once the baby is aged ≥ 1 h to allow for transition immediately after birth. This is in recognition of the large physiological changes that take place following delivery and that the stability of a newborn aged < 1 h may change rapidly and not accurately reflect their subsequent clinical trajectory. Trained study staff will ascertain chronological age and relevant pregnancy details by examining source documents and/or conducting a standardised maternal interview. Weight will be measured using the Seca™ 384 electronic weighing scale. A focused examination will be conducted to assess for the presence of major congenital malformations, severe jaundice and seizures.

Neonates for whom KMC is indicated per WHO guidelines (i.e. are considered 'stable') will be excluded and receive KMC as part of standard care (Fig. 3a, 'Stable to receive KMC'). Neonates for whom the indication for

Table 1 Characteristics of Ugandan trial hospitals, with resource availability in February 2019

	Entebbe Hospital	Iganga Hospital	Jinja Hospital	Masaka Hospital
Facility level of care	Regional	District	Regional	Regional
Catchment area [32]	Semi-urban	86% rural	86% rural	65% rural
Local poverty incidence (%) [32]	7.5	42.1	42.1	24.3
Live births (2018)	5706	6894	5287	9588
Neonatal admissions (2018)	597	933	698	2016
Born at an outside facility (n (%))	12 (2)	32 (3)	98 (14)	504 (25)
Birthweight < 2500 g (n (%))	248 (42)	421 (45)	234 (34)	NA[a]
Birthweight < 1500 g (n (%))	229 (38)	114 (12)	115 (17)	NA[a]
Average length of stay (days)	21	3–4	7	4
Paediatrician	1	1	3	2
Nurses in neonatal unit	8[b]	5	9	6
Overhead radiant heater	3 functional	1 functional	4 functional	2 functional
Incubator	2 functional	4 functional	3 functional, 6 non-functional	3 functional
Open cots	0	7	10	8
Oxygen supply	2 concentrators, 2 cylinders	1 concentrator, 1 cylinder	4 concentrators, 3 cylinders	2 non-functional concentrators, 1 cylinder
Bubble CPAP (improvised)	1	1	1	0
Pulse oximeter	0	1	4	1
Phototherapy	2 functional	1 functional, 1 non-functional	3 functional	4 functional
KMC beds, chairs	4 beds (KMC room), no chairs	5 beds (3 KMC room, 2 postnatal corner), no chairs	4 beds (KMC room), 20 chairs (neonatal unit)	4 beds (KMC room), no chairs

CPAP continuous positive airway pressure, *KMC* kangaroo mother care, *NA* not applicable
[a] Neonatal admissions data were not available for Masaka Hospital
[b] The neonatal unit at Entebbe Hospital has six government-employed nurses and two volunteer nurses

KMC is 'uncertain' per WHO guidelines (i.e. are 'prior to stability') will be further assessed. For those neonates who are found to meet eligibility criteria (Fig. 3a, 'Screening for eligibility'), a trained member of the study staff will monitor HR and SpO_2 using a Masimo Rad-8© pulse oximeter for 10 min and measure respiratory rate manually by counting breaths for 1 min. Those found to meet the criteria for 'life-threatening instability' (Fig. 3a, 'Too unstable'), or who have seizures or jaundice requiring treatment, will not be eligible for immediate recruitment and will enter a cycle of reassessment every 3 h. All will continue to receive clinically indicated treatments and cardiorespiratory monitoring at the discretion of the on-duty paediatrician, medical officer or nurse. If, during any reassessment within the first 48 h, a neonate is found to have improved and no longer meets exclusion criteria, recruitment may proceed. Neonates who continue to have life-threatening instability or meet other exclusion criteria by 48 h will be permanently excluded.

Informed consent

Written informed consent will be sought from the parents of all participants for the following: neonatal inclusion in the study; collection of sociodemographic and clinical data; and randomisation to a study arm. Consent will also be obtained for the possibility that the caregiver will provide continuous skin-to-skin contact, if randomised to that arm. Additionally, consent will be obtained for the collection of household socioeconomic and cost data, as well as data on infant–caregiver attachment and women's wellbeing. Study medical officers or nurses will request informed consent. The preferred person to provide informed consent for neonatal involvement is the mother. If a mother is unavailable or too ill to provide consent, consent can be obtained from the father. Once the mother is available and feeling well enough, the informed consent process will be repeated to confirm her consent for her baby's continued participation. An impartial and literate witness will be used during consent for non-literate parents, as per International Council for Harmonisation-Good Clinical Practice (GCP) guidance.

Collection of baseline data

Study staff will be trained in infection prevention and standard operating procedures (SOP) will detail infection

				STUDY PERIOD										
	Enrolment	Baseline assessment	Allocation	Post-allocation										Close-out
			0	T_0[1]	T_6	T_{12}	T_{18}	T_{24}	D_2	D_3	D_7	D_{14}	D_{21}	D_{28-30}
ENROLMENT:														
Eligibility screen	X													
Informed consent	X													
Allocation			X											
INTERVENTIONS:														
Intervention (KMC)				♦	—	—	—	—	♦					
Control				♦	—	—	—	—	♦					
ASSESSMENTS:														
Clinical review[2]				♦	—	—	—	—	♦					
Heart rate[3,4]	X			X	X	X	X	X	X	X				
Oxygen saturation[3,4]	X			X	X	X	X	X	X	X				
Temperature[4]		X		X	X	X	X	X	X	X				
Respiratory rate[4]		X		X	X	X	X	X	X	X				
Blood glucose[5]		X		X	X	X	X	X	X	X				
Physical examination		X		♦	—	—	—	♦						
Gestational age		♦	—	—	—	—	—	—	♦					
Weight[6]	X									X				X
Crown-foot length		♦	—	—	—	—	—	—	♦		X	X	X	X
Head circumference		X									X	X	X	X
Socioeconomic data[7]		♦	—	—	—	—	—	—	♦					
Cranial ultrasound[8]				♦	—	—	—	♦		X	X			X
WCI questionnaire[9]		♦	—	—	—	—	—	—	♦					X
MIRI questionnaire[10]														X
Outcome variables:														
All-cause mortality											X			X
Hypothermia								X						
Time to death/stability			♦	—	—	—	—	—	—	—	—	—	—	—
Time to exclusive breastmilk feeding			♦	—	—	—	—	—	—	—	—	—	—	—
Duration of admission[11]				♦	—	—	—	—	—	—	—	—	—	—
Readmission frequency														X
Daily weight gain														X
Women's well-being[9]														X
Infant attachment[10]														X

Fig. 2 OMWaNA trial schedule of enrolment, interventions and assessments [1]. The start of trial procedures (time 0) is defined as when the pulse oximeter is attached for cardio-respiratory monitoring [2]. All participants are reviewed daily while admitted to the hospital [3]. All participants receive continuous monitoring of heart rate (HR) and oxygen saturation (SpO_2) for 72 h after randomisation. Continuous monitoring continues until participants no longer require any form of respiratory support [4]. HR, SpO_2, axillary temperature and respiratory rate are measured every 6 h until stability criteria are met, after which the frequency transitions to daily [5]. Blood glucose is measured daily and may be discontinued once the participant tolerates full enteral feeds [6]. Participants are weighed on day 5, then daily until discharge (unless deemed too unstable by site study staff) [7]. Socioeconomic data, including household details, are collected within 48 h of enrolment. During this time, study staff also inform families that they will be asked about their household expenditures and activities over the coming month [8]. For participants at Entebbe and Jinja Hospitals, cranial ultrasounds are performed on days 1, 3 and 7 of hospitalisation (or as an outpatient if discharged before day 7) and on follow-up at day 28–30 [9]. The Women's Capabilities Index (WCI) is administered to all mothers within 48 h of enrolment and on days 28–30 to assess women's wellbeing [10]. The Maternal Infant Responsiveness Instrument (MIRI) is administered on days 28–30 to assess infant-caregiver attachment [11]. Duration of admission is measured as the mean time (days and hours) from hospital admission to discharge

control measures for the use of study equipment to avoid contamination between participants. Axillary temperature will be measured with a digital thermometer in degrees Celsius; three measurements will be taken to enable calculation of the mean value. Respiratory rate will be measured manually by counting breaths for 1 min. Blood glucose will be measured with a capillary sample using the study glucometer. Head circumference (HC) will be measured and a physical examination will be conducted. Baseline clinical and anthropometric data will be collected as soon

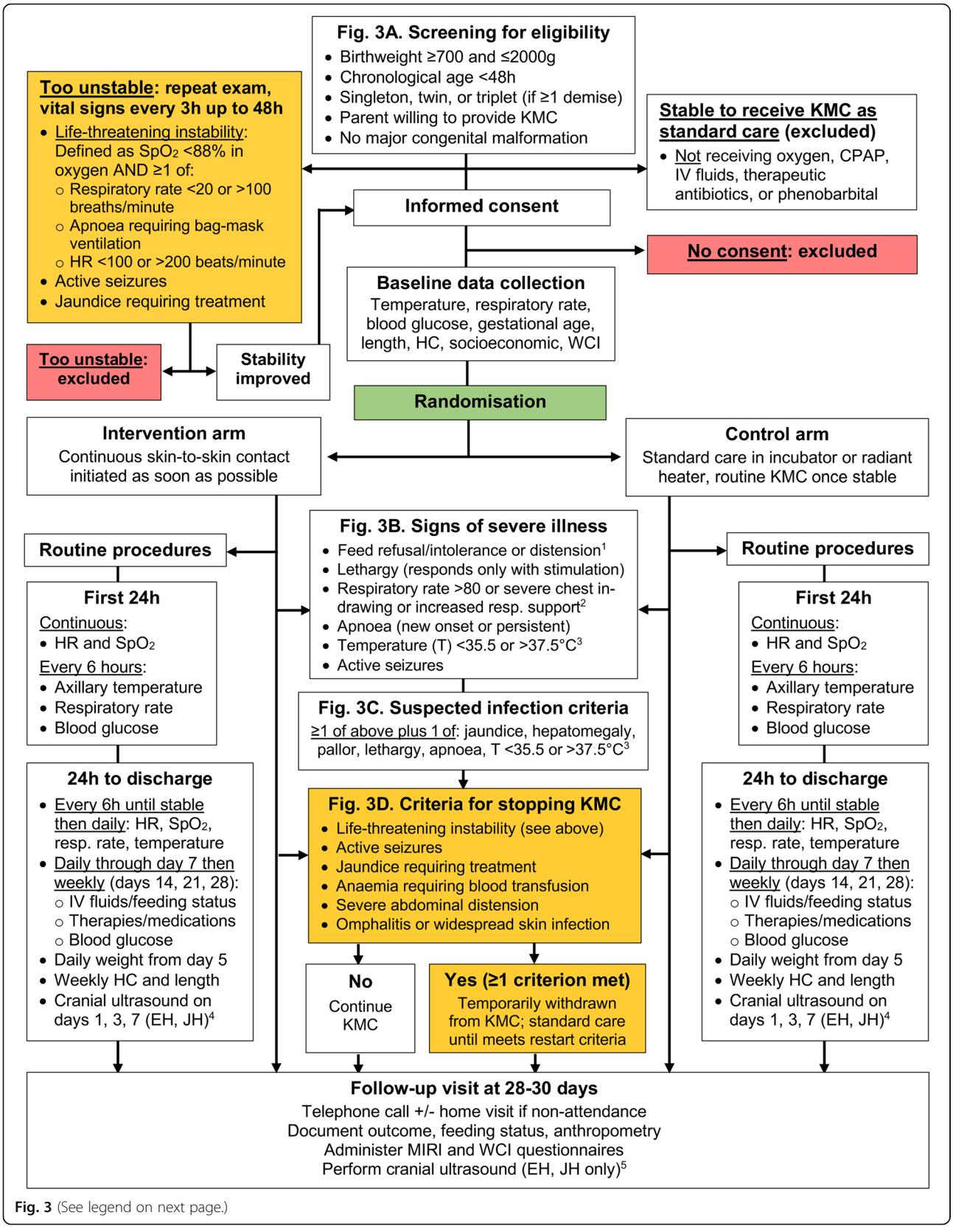

Fig. 3 (See legend on next page.)

(See figure on previous page.)
Fig. 3 Overview of trial flow including routine procedures and key criteria for eligibility screening, assessing severe illness and stopping KMC [1]. Refusal to feed, feed intolerance or abdominal distension (after starting feeds) [2]. Increased respiratory support defined as new oxygen or CPAP requirement [3]. Axillary temperature < 35.5°C after 1 h of observed skin-to-skin contact, not associated with environment or with hypoglycaemia [4]. For participants at EH and JH, cranial ultrasounds will be performed on days 1, 3 and 7 of hospitalisation (or as an outpatient if discharged before day 7) and on follow-up at days 28–30. CPAP continuous positive airway pressure, EH Entebbe Hospital, HC head circumference, JH Jinja Hospital. **a** Screening for eligibility. **b** Signs of severe illness. **c** Suspected infection criteria. **d** Criteria for stopping KMC

as possible after enrolment, with the exception of gestational age and crown-foot length, which may be delayed to within 48 h of enrolment. Gestational age will be estimated using Ballard score [34], last menstrual period and foot length [35]. Length will be measured using the Seca™ 210 neonatal measuring mat.

Socioeconomic data, including household details, will be collected within 48 h of enrolment using standardised parent interviews. The Women's Capabilities Index (WCI) questionnaire will also be administered to mothers during this timeframe. Study staff will also inform families that, over the coming month, they will be asked about their expenditures and the activities of members of their household in order to evaluate the economic impact of KMC relative to standard care.

Randomisation, allocation and blinding

Treatment allocation is random in a 1:1 ratio between groups using permuted blocks of varying block sizes. The allocation sequence was computer-generated centrally at MRC/UVRI by an independent statistician, stratified by birthweight (< 1000, 1000–1499 or ≥ 1500 g) and recruitment site. The random allocation sequence is uploaded onto the REDCap (Research Electronic Data Capture, Nashville, TN, USA) platform [36] and accessed using a computer with Internet access at each site. The randomisation server and research database are hosted at the MRC/UVRI and LSHTM Unit data centre. This precludes any possibility of study staff viewing the allocation sequence. Allocation is revealed only after the study medical officer or nurse has entered all required screening data into REDCap. The mother is the unit of randomisation; twin and triplet participants will be allocated to the same arm. Each site has one spare computer in case of breakdown or theft; if both fail, the site will revert to random allocation using telephone as the back-up option. Given the nature of the KMC intervention, blinding parents/caregivers is not possible. Process and outcome data will be anonymised and all analyses will be blinded. Analyses will be unblinded for the Data and Safety Monitoring Board (DSMB) at their request.

Intervention arm

Neonates in the intervention group will receive KMC initiated as soon as possible after randomisation. Neonates will be naked except for hat and diaper, and will be secured to the exposed chest of the caregiver using a KMC wrap (Fig. 4a). The caregiver is seated or lying on a bed, while the neonate receives any clinically indicated therapies (e.g. IV fluids, antibiotics, oxygen). Caregivers will be encouraged to provide KMC as close to continuously as possible, aiming for at least 18 h per day. If the primary caregiver is unavailable, another family member (e.g. father, grandmother) or close friend (helper) will be encouraged to provide KMC. If a family member or helper is not available to continue KMC, the neonate will be placed into an incubator or under a radiant heater until the caregiver returns. KMC will continue to be encouraged until discharge and at home after discharge, as per WHO guidelines. KMC is commonly practiced until the baby is 2500 g or resists the KMC position, which is often at 4–10 weeks after birth.

Neonates who meet any of the criteria for stopping KMC (Fig. 3d, 'Criteria for stopping KMC') will be temporarily withdrawn from the intervention and cared for in an overhead heater or incubator at the discretion of the on-duty paediatrician. KMC may be restarted once all of the following criteria are met: (1) no longer meet any of the stopping criteria; (2) no apnoea requiring bag-mask ventilation for 24 h; (3) not on phototherapy; (4) no seizures for 24 h; (5) no abdominal distension; (6) caregiver available and willing to do KMC; (7) no healthcare worker concerns about clinical condition.

Control arm

Neonates in the control group will be cared for in an incubator (Fig. 4b) or under a radiant heater. Caregivers are able to touch, hold and feed their baby, but may not provide any skin-to-skin contact until the neonate meets WHO criteria for KMC, i.e. are considered 'stable'. Neonates will be considered stable when the following criteria have been met for a continuous period of ≥ 24 h: (1) breathing spontaneously with $SpO_2 > 90\%$ in room air; (2) no need for supplemental oxygen or CPAP; (3) respiratory rate 40–< 60 breaths/min; (4) no apnoea; (5) HR 80–< 180 beats/min; (6) axillary temperature 36.0–37.4 °C; and (7) no need for IV fluids. These criteria are consistent with those being used in the WHO-led Immediate KMC (I-KMC) trial [37]. Once stable, neonates can transition to routine (intermittent) KMC with the caregiver in line with standard care at the

Fig. 4 OMWaNA intervention (KMC) and control (standard incubator care) arms. Images: University of California San Francisco Preterm Birth Initiative, with caregiver consent for publication (**a**); Melissa Medvedev (**b**)

trial sites. As in the intervention arm, neonates in the control arm who meet any of the criteria for stopping KMC (Fig. 3d, 'Criteria for stopping KMC) will be cared for in an overhead heater or incubator until re-start criteria are met.

Participant flow around study sites

Participant flow around the study sites is illustrated in Fig. 5, using Entebbe Hospital as an example. All neonates are initially stabilised and assessed at a radiant heater. While clinically 'unstable', neonates allocated to KMC are cared for in a study bed and those allocated to standard care are cared for in an incubator or radiant heater. Participants in both arms are transferred to the KMC step-down unit once they meet stability criteria.

Neonatal care capacity building

Substantial expansion of neonatal care capacity and infrastructure at all trial sites has been embedded within the OMWaNA trial. This includes enlargement of the KMC areas within the neonatal units to ensure

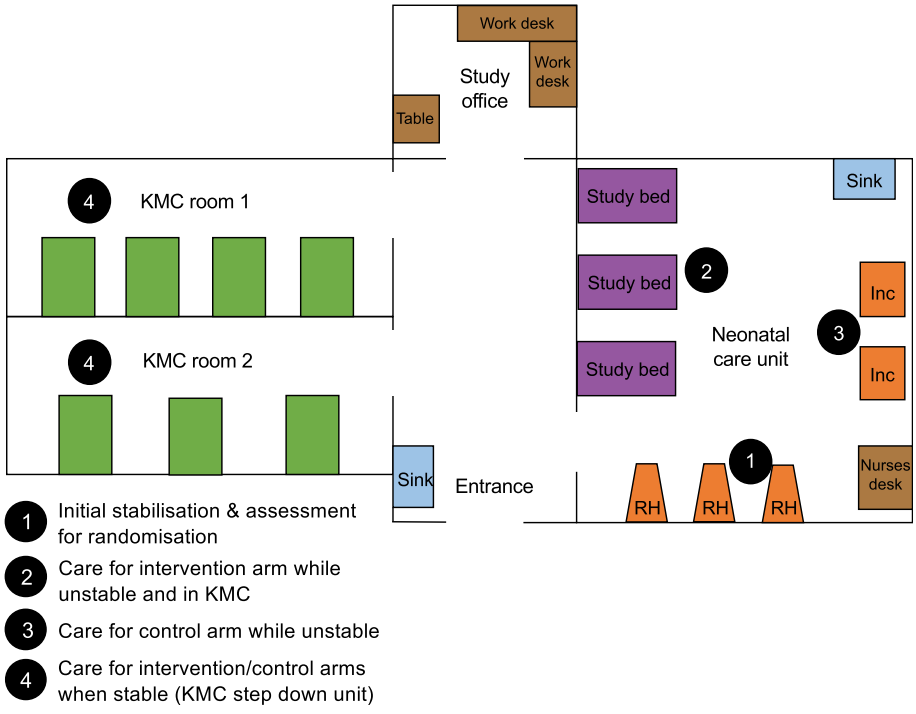

Fig. 5 Study site participant flow for the OMWaNA trial. Inc incubator, RH radiant heater

that all neonates, whether in KMC or not, can be cared for safely. Additional infrastructure improvements include sinks to provide an optimal environment for infection control, bathrooms/toilets for mothers/caregivers and office space for clinical staff. One study medical officer and 4–5 study nurses have been recruited to join the clinical teams at each site. Further, each site will be provided with the following supplies and equipment: six Masimo Rad-8© oximeters with neonatal sensors; one oxygen concentrator; two thermometers; one glucometer with blood glucose testing strips; one neonatal ventilation bag and mask; one Seca™ 384 neonatal weighing scale; one Seca™ 210 neonatal measuring mat; 2–3 paediatric stethoscopes; and a minimum of four adjustable beds. In addition, KMC wraps will be provided to support practice in each unit.

Clinical care for neonates in both arms

Clinical monitoring

All participants will be evaluated at least once by a study paediatrician or medical officer during the first 24 h after randomisation. All participants will receive continuous monitoring and recording of HR and SpO_2 for 72 h after randomisation. Continuous monitoring will continue until participants no longer require any form of respiratory support. HR, SpO_2, axillary temperature and respiratory rate will be measured and recorded by a study nurse every 6 h until stability criteria are met, after which the frequency will transition to daily. According to the same frequency, a study nurse will observe and record the presence or absence of clinical signs of respiratory distress, including chest in-drawing, nasal flaring and grunting. Blood glucose will be measured every 6 h during the first 24 h after randomisation unless it is < 2.6 mmol/L, in which case it will be measured hourly until two or more consecutive readings are in normal range (2.6–6.9 mmol/L). Subsequently, blood glucose will be measured daily until a participant is tolerating full enteral feeds.

Medical therapies

All enrolled neonates will receive clinically indicated treatments, including but not limited to oxygen, IV fluids (given by bolus or burette), antibiotics, aminophylline, anticonvulsant medicines and phototherapy. Standardised clinical guidelines will be followed for common neonatal conditions, including preterm fluids/feeding (including breastfeeding), suspected and proven sepsis, respiratory distress, jaundice and seizures. Bubble CPAP will be provided at the discretion of the on-duty paediatrician at sites where this is the standard of care. Jaundice will be treated with phototherapy for neonates in both arms. All caregivers will be trained in KMC regardless of study arm.

Clinical deterioration

Neonatal unit staff at all sites will be trained to recognise signs of severe illness (Fig. 3b, 'Signs of severe illness) and to inform study staff if a participant meets any of these criteria. The study paediatrician or medical officer (or study nurse if neither is present) will examine the neonate as soon as possible to assess whether signs of early-onset (< 72 h of age) or late-onset (≥ 72 h of age) infection (Fig. 3c, 'Suspected infection criteria') are present. Neonates will be reassessed for signs of severe illness and infection during daily rounds. Where available, a blood culture will be obtained as soon as possible if a neonate meets criteria for suspected infection; however, this will not delay administration of antibiotic therapy. Study staff will also assess if the neonate meets criteria for temporary withdrawal from KMC (Fig. 3d, 'Criteria for stopping KMC'). At the discretion of the study paediatrician, neonates may be referred to a higher-level facility for more specialised care; however, existing data indicate that this is an uncommon occurrence.

Discharge and follow-up

At the time of discharge, all caregivers will be provided with an illustrated handout on neonatal danger signs and instructed to contact the site study team or seek medical help if their baby becomes unwell. Caregivers of babies in both arms will be encouraged to continue KMC at home. All participants will be given an appointment to attend the follow-up clinic at the respective study site on days 28–30. At this visit, cranial ultrasound (Entebbe and Jinja Hospitals only) and anthropometry will be performed, feeding practices and outcomes (alive, dead, readmitted) will be documented, and the WCI and Maternal Infant Responsiveness Instrument (MIRI) questionnaires will be administered to mothers.

If participants are discharged before day 7, additional follow-up will be arranged according to study site. If participants do not attend the follow-up visit, a telephone call will be made the same day to ascertain outcome and feeding practices and to arrange follow-up, either in the clinic or at the families' home, as soon as possible. Routine follow-up beyond the planned study follow-ups will be provided by the study staff according to standard practice and based upon the clinical need of the baby.

Safety reporting and study monitoring

Adverse events (AE) are medical events or laboratory findings, which result in a change in clinical management after randomisation and until 28 days after birth. A serious adverse event (SAE) is defined as an event that

results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, results in persistent or significant disability, or requires intervention to prevent permanent impairment or damage [38]. Study medical officers and nurses will inform the site paediatrician about any SAE occurrence within 24 h. SAEs will be followed up by the paediatrician until their resolution or stabilisation, or until causality is determined to be unrelated to the trial intervention. If a serious *but unexpected* AE occurs, which might be related to the trial intervention, a SAE report will be submitted to the Research Ethics Committees (REC) at UVRI and LSHTM within 48 h of the investigators becoming aware of the event, with a follow-up report provided within a further five working days. This expedited reporting will be limited to those outcomes not already listed as primary or secondary outcomes, yet which might reasonably occur as a consequence of the trial intervention. All SAEs will be reported to the Sponsor and RECs as part of their respective annual progress and safety report.

The DSMB will oversee the overall integrity of the study, its safety and its continued relevance and ability to answer the primary objective. DSMB members include a perinatal epidemiologist/statistician (chair), a South African neonatologist and a neonatal bioethicist. The DSMB will receive a summary of SAEs after one month of recruitment, then move to every three or six months; the DSMB will decide the frequency following the first report. An interim analysis will be performed on the primary outcome when approximately half of neonates have been randomised. An independent statistician will perform the interim analysis, blinded to treatment allocation and report to the DSMB. Analyses will be unblinded at the request of the DSMB. In light of these data and other evidence from relevant studies, the DSMB will inform the Trial Steering Committee (TSC) if in their view: it is evident that no clear outcome will be obtained with the current trial design; they have a major ethical or safety concern; or it is evident that the intervention is clearly superior and continuing the trial would be unethical to those in the control arm. The TSC will make the final decision on study continuation.

The study will be monitored by the Reciprocal Monitoring Scheme of the East African Consortium for Clinical Research in collaboration with the Research Compliance and Quality Assurance section of the MRC/UVRI and LSHTM Unit. Dedicated study monitors, independent of the study team, will oversee progress and ensure the trial is conducted and data are handled in accordance with the protocol, SOPs and applicable ethical and regulatory requirements. In addition, the UVRI REC will conduct initial site visits with neonatal specialists from the Uganda Paediatrics Association and the Ugandan Ministry of Health Newborn Steering Committee. The trial may be subject to audit by LSHTM under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

Outcome measures

The primary outcome is all-cause early neonatal mortality (within seven days). Estimates suggest that three-quarters of neonatal deaths occur in the first week of life [2].

Secondary outcomes are as listed below.

1. *Prevalence of hypothermia (axillary temperature < 36.5 °C) at 24 h after randomisation*
   Axillary temperature will be assessed using a digital thermometer.
2. *Time from randomisation to clinical stabilisation (days and hours)*
   The date and time of randomisation and clinical stabilisation will be prospectively recorded. Stability is defined as having met all of the following criteria for a continuous period of at least 24 h:
   - Breathing spontaneously with SpO_2 > 90% in room air;
   - No need for supplemental oxygen or CPAP;
   - Respiratory rate 40– < 60 breaths/min;
   - No apnoea;
   - HR 80– < 180 beats/min;
   - Axillary temperature 36.0–37.4 °C;
   - No need for IV fluids.
3. *Time from randomisation to death (days and hours)*
   The date and time of death will be prospectively recorded from the death certificate for in-hospital deaths. For deaths occurring after discharge, the date will be recorded according to verbal report by the parent/caregiver.
4. *Time from randomisation to exclusive breastmilk feeding (days and hours)*
   The date and time of randomisation and initiation of exclusive breastmilk feeding will be prospectively recorded. Exclusive breastmilk feeding is defined as receiving breastmilk, either directly from the breast or by nasogastric tube, bottle, cup or spoon after expression from the breast, as the sole source of nutrition [39].
5. *Mean duration of hospital admission (days and hours)*
   The date and time of admission and discharge will be documented prospectively for the first admission episode.
6. *All-cause mortality within 28 days*
   This outcome will be documented at the follow-up visit on days 28–30. If participants do not attend, a telephone call will be made the same day to ascertain outcome.
7. *Mean frequency of readmission at 28 days*

Episodes in which a neonate who had been discharged from a hospital is readmitted to the same hospital during the first 28 days will be prospectively recorded. Episodes in which a neonate is readmitted to a different hospital will be recorded according to verbal report by the parent/caregiver on follow-up at days 28–30.

8. *Mean daily weight gain (g/day) at 28 days*
   Mean daily weight gain will be calculated as the difference between weight at enrolment and on follow-up at days 28–30, as measured by the study scale.
9. *Women's wellbeing at 28 days*
   Women's wellbeing will be assessed using the WCI, a capability-based composite measure of quality of life that will capture the broader effects to the mother of practicing KMC. The WCI includes six domains (physical strength, inner wellbeing, household wellbeing, community relations, economic security, happiness), with a total of 26 sub-dimensions [40]. Developed and validated in Malawi, the WCI was recently adapted for use in Uganda [41].
10. *Infant–caregiver attachment at 28 days*
    Infant–caregiver attachment will be assessed using the MIRI, a 22-item questionnaire that measures maternal recognition of responsiveness to infant cues, maternal recognition of infant responsiveness and difficulties in responsiveness [42]. The MIRI was developed and validated in the United States, and is now being used in Uganda [43].

Process outcomes

Understanding the hypothesised causal pathways for clinical effects of the intervention (objective 3) will be achieved by measurement of the following process outcomes, which are categorised as providing very early (within 24 h), early (within 72 h) or late clinical impact.

1. *Cardiorespiratory stability within 24 h, 72 h after randomisation*
   Proportion of time spent with suboptimal HR (< 100 bpm) and SpO_2 (< 85%) over the first 24 h and 72 h after randomisation, measured and recorded continuously using the study pulse oximeter.
2. *Prevalence of hypothermia (axillary temperature < 36.5 °C) at 24 h, 72 h after randomisation*
   Axillary temperature will be assessed using a digital thermometer.
3. *Hypothermia density within 24 h, 72 h after randomisation*
   Hypothermia density is defined as the proportion of time the axillary temperature is < 36.5 °C during a defined time period. Axillary temperature will be measured every 6 h during the first 24 h after randomisation and until clinically stable, after which it is measured daily.
4. *Prevalence of hypoglycaemia (blood glucose < 2.6 mmol/L) within 24 h, 72 h after randomisation*
   Blood glucose will be measured using a study glucometer and glucose testing strips.
5. *Presence and severity of IVH at 72 h, seven days after randomisation; presence of late intracerebral sequelae of prematurity at days 28–30*
   IVH is a complication of prematurity characterised by bleeding within the cerebral ventricles, typically originating from the periventricular germinal matrix; severity ranges from grade 1 (mild) to grade 4 (severe) [44]. Late intracerebral sequelae include cystic degeneration, post-haemorrhagic hydrocephalus and cerebral atrophy. The study paediatrician or medical officer at two of the four hospitals (Entebbe and Jinja) will perform cranial ultrasounds using a Sonosite Edge II© portable ultrasound machine. Both standard and linear probes will be used to assess for abnormalities according to a defined protocol and will include ≥ 11 coronal and sagittal views. Images will be read by an independent expert.

Data collection, management and security

Trial data will be electronically entered into trial-specific case report forms on tablets using an offline, mobile REDCap application, with inbuilt ranges and consistency checks. Data from tablets will be synchronised once daily over a secure connection with the web-based REDCap database, hosted at the MRC/UVRI and LSHTM Unit data centre. Cardiorespiratory data from Masimo Rad-8© oximeters will be downloaded using Stowood Visi-Download™ software, captured in CSV files, securely transmitted to MRC/UVRI, analysed with PROFOX™ software and reconciled with the trial database. Cranial ultrasound images will be stored in OsiriX Dicom™ software and interpreted blind to allocation and clinical details. Logs linking parent/caregiver names and residence location will be stored separately on password-protected computers, with a hard copy stored in locked cabinets in secure rooms at all sites.

All data will be stored in institutional servers at the MRC/UVRI and LSHTM Unit during the study. Data from the web-based REDCap database will be downloaded and stored on institutional servers at LSHTM in London for access by the PIs and independent statistician for analysis and preparation of reports for the DSMB, respectively. These secure, password-protected servers are only accessible within the LSHTM network and activity is fully audited, recording both login details and file system access. Access will be limited to essential research personnel.

Sample size

Assuming a control mortality rate of 25% across the four recruitment sites, 1750 neonates (875 per arm) would enable us to detect a relative difference between arms of 22.4% (5.6% absolute difference) with 80% power and a significance level of 5%. If the control mortality rate were in fact as low as 18%, we would still be able to detect a relative difference of 27% (absolute difference of 4.8%). We plan to recruit 2188 neonates (1094 per arm) in order to allow for 10% withdrawal due to clinical deteriorations and consent withdrawal, and 10% dilution due to non-compliance and loss to follow-up. This sample size would enable us to detect absolute reductions of 6.3% and 5.4% from control rates of 25% and 18%, respectively, with 90% power.

Statistical analyses

Summary of baseline data and flow of patients

Baseline characteristics of enrolled neonates will be summarised by treatment arm. Descriptive statistics for continuous variables will include mean, standard deviation, median, range and number of observations. Categorical variables will be summarised as counts and proportions. Participant flow through screening, randomisation, allocation and follow-up will be illustrated in a CONSORT diagram (Fig. 6), with reasons for exclusion, non-adherence, loss to follow-up and non-analysis documented.

Primary and secondary outcome analyses

Primary and secondary outcome analyses will be carried out on all neonates as randomised ('intention-to-treat'). The rate of loss to follow-up will be reported. We will report risk ratios for mortality within seven days (primary outcome) and 28 days (secondary outcome) for intervention versus control with associated 95% confidence intervals (CI). Time from randomisation to death, time from randomisation to exclusive breastmilk feeding and length of stay will be analysed using Kaplan–Meier plots and hazard ratios, with accompanying 95% CI calculated using Cox proportional hazards regression. All other secondary outcomes will be analysed using appropriate regression models accounting for the nature of the distribution of the outcome, and results will be presented as appropriate effect sizes with a measure of precision (95% CI). Both unadjusted analyses and analyses adjusted for stratification factors will be carried out. Additional exploratory analyses will control for any baseline measures that appear to be imbalanced between arms.

Subgroup and adjusted analyses

Subgroup analyses are planned to explore between-group differences in the impact of KMC relative to standard care on mortality by gestational age (< 28, 28–32 or > 32 weeks), birthweight (< 1000, 1000–1499 or ≥ 1500 g) and recruitment site. Gestational age is an important predictor of newborn survival. In settings with newborn special care without intensive care, such as the four trial hospitals, neonatal mortality rates are 86% in neonates born at < 28 weeks and 41% in neonates born at 28–31 weeks [45]. Further exploratory analyses will be carried out to explore the association between mortality and time of initiation (< 12, 12– < 24 or ≥ 24 h), and continuity of KMC (median hours per day: < 6, 6– < 12, 12– < 18 or 18–24 h).

Process evaluation

The process evaluation is being conducted to strengthen understanding of KMC initiation before stabilisation on neonatal health outcomes, considering both intended (beneficial) and unintended (negative) clinical effects. Changes in neonatal care between hospitals and from before the trial will also be assessed. This evaluation will be conducted in accordance with the MRC guidance on process evaluation of complex interventions [46], and will integrate quantitative and qualitative data. Quantitative outputs will include data related to causal pathways for clinical effects, neonatal admissions data, and health system- and facility-level survey data. Quantitative data will be summarised using descriptive statistics. Qualitative data will be collected though in-depth interviews, focus group discussions and workshops with parents/caregivers, healthcare providers and other key stakeholders to identify experiences of KMC and explore facilitators and barriers to inform uptake and sustainability. These data will be analysed using a thematic content approach. An iterative methodology will be used with data collected at several time points and then used to inform later explorations. Intervention reporting will follow the template for intervention description and replication (TIDieR) [47], which will ensure a shared understanding of all activities related to the trial intervention and, if shown to be effective, how these relate to any proposed scale-up activities. In addition, the TIDieR will facilitate thoughtful consideration regarding the transferability of findings outside a trial setting and to other hospitals in Uganda and elsewhere.

Economic evaluation

The incremental cost, cost-effectiveness, budget impact and equity of KMC for neonates before stabilisation relative to standard care will be examined from both an aggregated and a disaggregated societal perspective (provider and household combined), in accordance with the reference case [48]. Effects of the intervention on neonatal health and maternal wellbeing will be assessed. Both financial costs, which reflect actual monies paid,

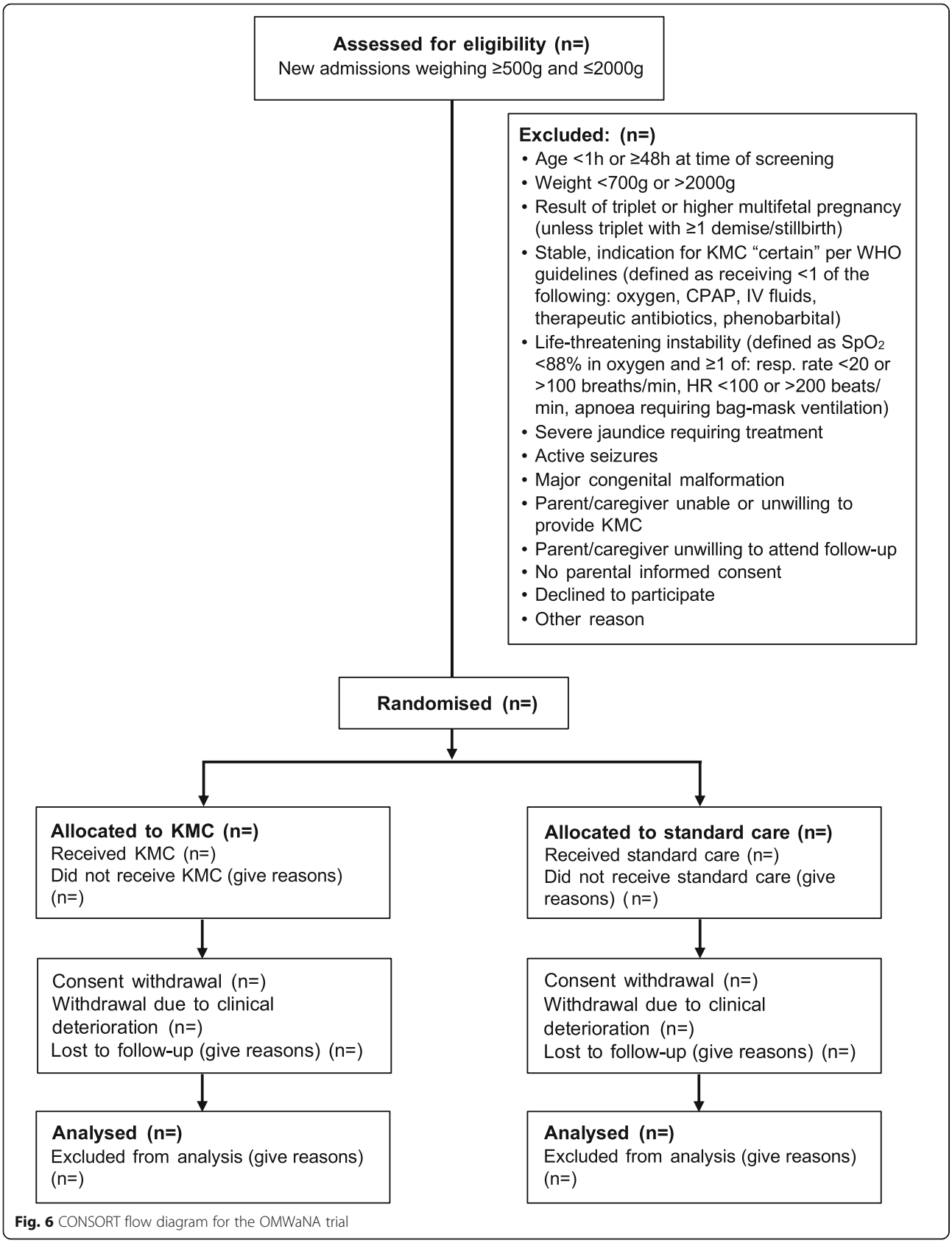

Fig. 6 CONSORT flow diagram for the OMWaNA trial

and economic costs, which reflect the full value of resources used, will be examined. Multiple data sources will be triangulated to arrive at best estimates. Where possible, resource use and unit costs will be collected and presented separately, although some costs, such as out-of-pocket payments for transport, do not permit this. Household costs will be collected through surveys amongst a sample of caregivers at the time of discharge and during follow-up visits. Costs to providers will be collected prospectively and retrospectively using project accounts, key informant interviews, facility audits, direct observations and time-use surveys. As necessary, secondary data on costs of treating subsequent conditions may be supplemented with limited primary data collection in the trial hospitals. Costs and effects will be modelled using a lifetime time horizon.

Discussion

Deaths in the neonatal period are responsible for 47% of mortality in children aged < 5 years [1]. Complications of prematurity are the leading cause, accounting for 35% of neonatal deaths and 16% of under-5 deaths [1]. The majority of neonatal deaths occur before stabilisation in settings without intensive care [2]. The OMWaNA trial will measure the impact of KMC initiated before stabilisation on mortality within seven days at four neonatal units in Uganda, where intensive care is not available. With rates of preterm birth and institutional delivery on the rise globally [5, 6, 49], this intervention has the potential to benefit an ever-growing number of neonates. This trial was designed with an aim to align clinical criteria and data definitions to facilitate future opportunities for pooled analyses with related RCTs, including the eKMC trial in The Gambia [50] and the multi-country I-KMC trial led by WHO [37]. Several challenges were identified over the course of designing the OMWaNA trial, the most notable of which are related to informed consent and recruitment, non-adherence and contextual resource limitations.

Challenge 1: timely recruitment with informed consent

Obtaining timely informed consent for this RCT may be challenging given the involvement of sick neonates [51, 52], the fact that KMC needs to be started as soon as possible after birth and the fact that some women may be too ill, especially within the first 24 h, to provide consent or participate. In addition, some of these women may not be literate. Parental stress is compounded by the fact that complications may be unexpected, especially in low-resource settings, where knowledge of preterm birth is generally low. To help address these issues, the OMWaNA trial utilises the continuous consent approach [53], which involves providing information at multiple time points both before and after recruitment. Studies have found that the validity of consent improves when discussion continues after recruitment [53]. This approach has three main elements:

1. Parents will be given preliminary information during neonatal eligibility screening;
2. If the neonate is eligible, a comprehensive information sheet will be provided, and further discussion will take place. If the parents express willingness and ability to participate, written informed consent will be obtained and the neonate will be randomised;
3. During the intervention period, study staff will meet with parents to ensure that they understand the trial procedures and wish to continue to participate in the trial. It will be made clear that they may withdraw their baby from the trial at any time.

Audit data from the feasibility study at Jinja Hospital suggest that ~ 400 eligible neonates are admitted annually [14]. Preliminary data suggest that ~ 500 eligible neonates each are admitted to Iganga and Entebbe Hospitals per year and ~ 800 eligible neonates are admitted to Masaka Hospital per year. Thus, a total population of ~ 4400 eligible neonates is expected over the 24-month recruitment period, which means a recruitment rate of ~ 50% will be required to achieve the target sample of 2188. The feasibility study findings suggest that this is realistic and achievable [14]. The trial timeline includes a three-month buffer period in the event that recruitment is delayed or slower than expected. Further, training of study staff emphasised the importance of timely reporting and responsiveness to recruitment issues.

Challenge 2: non-adherence to allocated treatment, especially continuous KMC

Among neonates in the control group, non-adherence with allocation (e.g. parents demanding early KMC) is a potential issue; however, this has not been reported in other trials [11]. Adherence in both arms, particularly the KMC arm, could be affected by parents witnessing a death (e.g. in the KMC position). Some babies will die regardless of the trial arm to which they are randomised. Preterm neonates can die quickly, even in settings with intensive care, and such deaths are a recognised impediment to KMC [54]. Stigma regarding preterm birth is common in Uganda, but has not impeded KMC practice for stable babies [55]. Study staff will counsel parents about the potential for mortality at the time of enrolment as well as counsel parents of neonates who die and those who witness a death. In addition, prompt reporting of all SAEs and trial monitoring through regular site visits will further facilitate timely identification of and responsiveness to any compliance issues, should they arise.

Adherence to the target duration of KMC (≥ 18 h/day) may be challenging [56]. Among five RCTs that promoted continuous KMC, three reported durations of ≥ 20 h/day [18, 57, 58] and two did not report duration [15, 59]. Among 16 RCTs evaluating intermittent KMC in stable neonates, one reported mean/median duration of 17 h/day, five reported 10–14 h/day and nine reported < 10 h/day [60]. The OMWaNA trial will employ a comprehensive approach to improve adherence. An illustrated KMC handout will be provided to caregivers at the time of enrolment. Study staff will counsel mothers about the benefits of KMC throughout the hospital stay, including the time of discharge. Studies have noted the importance of staff training and counselling for KMC [61, 62], and a related RCT demonstrated the efficacy of peer-counselling in promoting breastfeeding among hospitalised preterm neonates [63]. We will establish KMC peer-counselling programmes at each site, enlisting mothers who practiced KMC as participants when they return for follow-up. Peer counselling will address many maternal concerns and may help facilitate longer durations of KMC. We will also engage hospital administrators about KMC guidelines. Adjustable beds and KMC wraps will be provided, as these have been shown to improve adherence [56]. Lack of privacy and inadequate space for beds and equipment were identified as significant barriers to KMC practice in the feasibility study [14]. Provision of increased space within the four neonatal units may facilitate caregiver privacy as well as help improve clinical providers' ability to safely care for at-risk neonates. Despite these measures, this is a pragmatic trial and some non-adherence is inevitable. The effect of non-adherence might be to dilute the size of the effect of KMC (assuming it 'works') and this has been factored into the sample size calculations. Biannual neonatal quality of care surveys, including progress monitoring of KMC provision/services, will be conducted at the four sites as part of the process evaluation.

Challenge 3: context including infrastructure, supplies and equipment

Over the six months preceding the start of the trial, the study team has made extensive efforts to expand neonatal care capacity at the four hospitals. Improvements include increased space and water supply in the neonatal units, office space for clinical staff, bathrooms/toilets for caregivers, adjustable beds for KMC, and various equipment and supplies. Despite these efforts, context-related resource constraints are inevitable. In government facilities, such as the four trial hospitals, supply/medication shortages are common and repair of malfunctioning equipment (e.g. incubators, oxygen concentrators) is often protracted. Triannual (every four months) surveys of staffing, equipment, supply and medication availability, and infrastructure across the sites are included in the process evaluation. In addition to the supplies and equipment provided before trial commencement, the budget includes a small allowance to help cover the cost of necessary commodities for each participating neonate.

Electrical power is required for incubators, radiant warmers, oxygen concentrators and phototherapy. Lack of access to reliable electricity is a problem in many LMICs, including Uganda, where a 2007 national survey showed that only 19% of government hospitals had reliable electricity (during working hours) or a backup generator with fuel [64]. In 2014, a study at Jinja Hospital recorded 120 episodes of power failure (mean of 13 times/week), with a median duration of 30 min each, over a 64-day period [65]. The four trial hospitals have reliable power supply, with occasional brief power outages (e.g. when back-up generators run out of fuel). Daily communication between staff at the MRC/UVRI and LSHTM Unit and the sites will facilitate timely identification and resolution of any significant power outages impacting patient care. Frequency and duration of power outages will be recorded by site staff.

Conclusion

The OMWaNA trial will assess the effectiveness of KMC in reducing mortality among neonates before stabilisation, a population where the benefits of KMC are currently uncertain. These findings are expected to have broad applicability to hospitals in low-resource settings and important policy and programme implications. The trial will be among the first to rigorously compare the incremental cost and cost-effectiveness of KMC and standard care, taking into account family members' time, which will be crucial to ensure the sustainability of this intervention. Additionally, OMWaNA will advance understanding of the underlying mechanisms for the effects of KMC before stabilisation, including prematurity-associated brain injury, which could help inform prevention of disability as well as guide further innovation to improve survival for preterm newborns in the highest mortality settings.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-019-4044-6.

Additional file 1. SPIRIT checklist.
Additional file 2. LSHTM ethics letter.
Additional file 3. UVRI ethics letter.
Additional file 4. UNCST ethics letter.
Additional file 5. Funding documentation.

Abbreviations

AE: Adverse event; CI: Confidence interval; CONSORT: Consolidated Standards of Reporting Trials; CPAP: Continuous positive airway pressure; DSMB: Data

and Safety Monitoring Board; EH: Entebbe Hospital; GCP: Good Clinical Practice; HC: Head circumference; HR: Heart rate; IV: Intravenous; IVH: Intraventricular haemorrhage; JH: Jinja Hospital; KMC: Kangaroo mother care; LBW: Low birthweight; LMIC: Low- and middle-income countries; LSHTM: London School of Hygiene & Tropical Medicine; MIRI: Maternal Infant Responsiveness Instrument; MRC: Medical Research Council; OMWaNA: Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa; PI: Principal investigator; RCT: Randomised controlled trial; REC: Research Ethics Committee; SAE: Serious adverse event; SOP: Standard operating procedure; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; SpO_2: Oxygen saturation measured by pulse oximetry; TSC: Trial Steering Committee; UVRI: Uganda Virus Research Institute; WCI: Women's Capabilities Index; WHO: World Health Organization

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Composition, roles and responsibilities of the TSC, DSMB, TMG and Study Implementation Team
Trial Steering Committee:
Chair: Prof Elizabeth Molyneux, University of Malawi, Blantyre, Malawi (retired); *Members:* Prof Stefan Peterson, United Nations Children's Fund, New York, USA; Dr. Rebecca Nantanda, Uganda Paediatric Association, Kampala, Uganda; Prof Adriano Cattaneo, WHO Collaborating Centre for Maternal & Child Health, Trieste, Italy (retired); with invited observers from the Trial Management Group.
Role: Oversight of trial conduct and progress towards its objectives; review at regular intervals relevant information from other sources; receipt and review of DSMB reports with action as appropriate.
Data and Safety Monitoring Board:
Chair: Prof Maria Quigley, University of Oxford, Oxford, UK; *Members:* Dr. Natasha Rhoda, University of Cape Town, Cape Town, South Africa; Prof Maureen Kelley, University of Oxford, Oxford, UK.
Role: Monitor data for quality and completeness, and evaluate for any evidence of harm to participants.
Terms of the DSMB charter are available upon request from the OMWaNA PI (Prof Joy Lawn).
Trial Management Group:
Prof Joy Lawn (PI), Dr. Melissa Medvedev (co-PI), Dr. Peter Waiswa (co-PI), Dr. Cally Tann (co-PI), Prof Elizabeth Allen (co-PI), Prof Moffat Nyirenda (senior MRC/UVRI member), Prof Diana Elbourne (senior trial and ethics advisor), Dr. Victor Tumukunde (site coordinator), Dr. Ivan Mambule (trial coordinator), Dr. Elizabeth Ekirapa-Kiracho (lead economist), Dr. Catherine Pitt (economic advisor).
Role: Monitoring of study progress; advice; implementation, publications and dissemination strategy.
Study Implementation Team:
Drs Melissa Medvedev and Cally Tann (on behalf of TMG), Ms. Ruth Canter (on behalf of LSHTM Clinical Trials Unit), Drs Victor Tumukunde and Ivan Mambule (trial coordinators), Mr. Kenneth Katumba (economist).
Role: Review of study progress, including staff and resource issues; ensure study is administered in a financially responsible manner; report to the Ministry of Health on the study's progress and achievements, as necessary.

Trial status
Recruitment is expected to begin in November 2019 and continue until the last quarter of 2021.
Current protocol version and date
V2.0, 24th September 2019
Protocol revision chronology
V1.1, 17th May 2019 Original approved protocol
V1.2, 31st May 2019 Amendment 1 (minor, made in response to recommendations of the LSHTM REC)
Added details regarding the Public Liability ('negligent harm') and Clinical Trial ('non-negligent harm') insurance policies held by LSHTM that apply to this trial
V2.0, 24th September 2019 Amendment 2 (substantial, made in response to recommendations from the TSC, DSMB, TMG and MRC/UVRI REC):
Removed 'mother or neonate enrolled in another MRC/UVRI research project' as an exclusion criterion; clarified inclusion criterion regarding age at time of screening as '≥ 1 hour and < 48 hours;' changed inclusion criterion regarding place of birth to inborn or outborn; changed inclusion criterion regarding multiple births to 'singleton, twin, or triplet (triplet if demise or stillbirth of 1 or more fetuses); clarified that twins and triplets will be allocated to the same arm, if both are eligible; added study nurse as an additional member of site staff who may obtain informed consent and randomise participants; updated SAE reporting schedule per DSMB; changed secondary outcome regarding feeding to 'mean time from randomisation to exclusive breastmilk feeding;' changed other secondary timing-related outcomes to 'mean time from randomisation to…;' clarified secondary outcome regarding readmission to 'mean frequency of readmission at 28 days;' clarified that length, gestational age assessment, and initial WCI may be delayed to within 48 h of enrolment; changed frequency of surveys on staffing, equipment, and supplies to triannually (every four months); changed timing of process evaluation workshops to 6 months after recruitment begins; changed weight bands for stratification and subgroup analyses to < 1000, 1000–1499, or ≥ 1500 g; added exploratory analyses of association between mortality and time of initiation/continuity of KMC; added detail that KMC wraps will be procured locally per UVRI REC.
Trial sponsor
London School of Hygiene & Tropical Medicine (LSHTM)
Sponsor's reference: 2019-MUU-234
Contact name: Mrs. Patricia Henley
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The sponsor had no role in trial design, protocol/manuscript preparation, nor the decision to submit the manuscript for publication. The sponsor will play no role in trial conduct, management, or planned analyses, and does not have authority over any of the aforementioned activities. Participants will receive compensation for any harm suffered as a result of the trial, as per the sponsor's standard indemnity.

Authors' contributions
MMM and JEL conceived the trial. MMM and JEL prepared the Joint Global Health Trials funding application, with substantial input from CJT, EA, PW, DE and CP. MMM drafted the trial protocol, with substantial input from JEL, CJT, PW, RRC, HB, DE and EA. EEK, KK and CP designed the economic evaluation, with input from MMM and JEL. GG designed the women's wellbeing component, with input from EEK, KK and CP. IM, VT, RRC, KK, MMM and CJT prepared case report forms and SOPs, with input from PW, CHH, EEK, HB, DE, EA and JEL. MMM and JEL designed the process evaluation, with substantial input from CJT, VT, PW, JS and DE. The study protocol will be implemented by VT, IM, MMM, CJT, RRC and KK, with oversight by JEL, PW, EA, MN, DE, EE and CP. MMM drafted the manuscript. All authors participated in manuscript revision and approval of the final version.

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Shriver National Institute of Child Health and Human Development of the National Institutes of Health (#K23HD092611) is supporting Dr. Melissa Medvedev's work on the trial. The funders played no role in trial design nor the decision to submit the protocol for publication. The funders will not play a role in trial conduct nor in collection, analysis or interpretation of data.

Availability of data and materials

The final trial dataset will be available upon request to the PI or an institutional delegate. We plan to publish the results of the trial and the economic and process evaluations in peer-reviewed journals in an open access format. Manuscripts resulting from the trial will adhere to the Consort Guidelines and to authorship criteria set by the International Committee of Medical Journal Editors. We plan to present study results at international meetings and communicate findings to key audiences, including the WHO and the Ugandan Ministry of Health. Findings will be shared with relevant local stakeholders and participants' families, adapted for those affected by a death.

Ethics approval and consent to participate

Ethical approval for the study was obtained from the Research Ethics Committees of LSHTM (Additional file 2, reference: 16972), UVRI (Additional file 3, reference: GC/127/19/06/717) and the Uganda National Council of Science and Technology (Additional file 4, reference: HS 2645). Any substantial changes to the trial protocol which may impact on the conduct of the study or participant safety, will be submitted to the ethics committees and, following approval, subsequently notified to the Sponsor, TSC, DSMB and trial registry. Informed consent will be obtained from all participants. Procedures for obtaining informed consent are described in the main manuscript.

Consent for publication

Written consent for obtaining and publishing the photograph (Fig. 4a) was obtained from the caregiver.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

8. Discussion and implications

8.1. Scope of this chapter

In the preceding chapters, this thesis has presented the results of three studies and the protocol for a RCT that was informed by these studies, and discussed how they contribute to the existing evidence base. This chapter summarises the findings of the PhD and outlines the implications for inpatient care of small and sick newborns in the sub-Saharan African context, with a focus on KMC practice. Recommendations for policy, programmes, and future research will be presented in the final chapter.

8.2. Main findings of this PhD

The overall aim of this PhD has been to improve risk prediction amongst small and sick newborns and inform the design of a trial of KMC initiated before stabilisation in a sub-Saharan African context. Globally, there are 2.5 million neonatal deaths each year,[20] among which more than 80% occur in LBW babies who are small because they are preterm, SGA, or both.[23–25] Sub-Saharan Africa has experienced slow progress in reducing newborn deaths,[20] especially those due to complications of preterm birth.[15,30] The ARR for neonatal mortality in sub-Saharan Africa between 2000 and 2018 (2.1%) was less than half of the global ARR (4.3%) that will be required to achieve the SDG and ENAP targets by 2030 (Figure 1-1),[17–19] underscoring the need for improved quality of inpatient care and scale-up of effective interventions for small and sick newborns. Assessment of individual risk, using a simplified score feasible for use in LMIC facilities, could expedite recognition of severe illness and contribute to improvements in the effectiveness and efficiency of care delivered in such settings. Further, the effect of initiating KMC before stabilisation remains an unaddressed research priority and a well-designed RCT is needed to examine mortality impact,[37,62] particularly in settings without intensive care where the burden of neonatal death and disability is highest.[20,121,122]

The first objective of this PhD focused on utilising a clinical cascade model to assess facility readiness for neonatal care in East Africa. Cascades were developed for six common neonatal conditions and used to assess 23 health facilities in Kenya and Uganda. The second objective focused on quantifying in-hospital mortality risk among neonates weighing 2000g or less. A logistic model was derived and validated using data from 187 neonatal units in the UK (n=110176) and one hospital in The Gambia (n=550). The NMR-2000 score, which includes three

parameters that can be feasibly collected in LMICs, demonstrated very good discrimination and goodness-of-fit. The third objective of this PhD focused on evaluating the feasibility of initiating KMC before stabilisation amongst neonates ≤2000g at a Ugandan hospital. The study showed that it was feasible to monitor and provide care in the KMC position (n=10), and demonstrated the acceptability of this intervention amongst parents and care providers (n=20). An audit of admissions to the neonatal unit (n=254) found that the proposed therapy-based instability criteria were easily implementable. The fourth objective drew upon the findings of the first three objectives to inform the design of a RCT, which aims to determine the effect of KMC initiated before stabilisation on mortality within 7 days relative to standard care. The OMWaNA trial is now ongoing at four government hospitals in Uganda.

8.3. Cascade model to assess facility readiness for neonatal care in Kenya & Uganda

The clinical cascade model provides a novel approach to quantitatively assess the physical readiness of facilities to provide care for small and sick newborns. In contrast to widely used facility inventories and EmONC signal functions,[123–125] this model employs a stepwise approach that assesses the availability of resources needed to identify and manage six common neonatal conditions,[126,127] with a negligible increase in data collection requirements.[123,124] The cascade study estimated overall mean readiness of 26% across conditions and stages of care at the 23 facilities in Kenya and Uganda. Readiness was consistently lowest for the respiratory distress-apnoea cascade, with only 17-26% of facilities having all supplies required for identification. This was primarily due to the fact that a functional pulse oximeter was only available in 22-44% of facilities at both timepoints. In 2015, a study at 11 district hospitals in eastern Uganda similarly found that only one paediatric ward had a pulse oximeter, additionally reporting that 89% of paediatric nurses failed to demonstrate adequate skills in pulse oximetry.[128] In contrast, a recent evaluation at nine teaching hospitals across southern Asia and sub-Saharan Africa, including three in Kenya and one in Uganda, found that all facilities had pulse oximeters for neonatal care.[129] Overall readiness was higher amongst facilities with a NSCU (37%) relative to those without (20%), and facilities with a NSCU had significantly increased treatment readiness for essential newborn care, poor feeding-hypothermia, respiratory distress-apnoea, and infection-convulsions. These findings have implications for KMC practice and neonatal care more broadly, specifically the need to define physical resource requirements for facilities by level of care. This is in line with ENAP recommendations regarding indicators for neonatal inpatient care.[26,34,130] The cascade model identified a consistent pattern of 30-32% overall readiness loss across the 23 facilities. The majority of loss occurred in the identification stage; however, the poor feeding-hypothermia,

infection-convulsions, and essential newborn care cascades lost most readiness during the treatment stage in 2017. Together with low overall readiness, this variability underscores the need for improved supply chain management systems to enable more timely detection of resource shortages. The cascade model provides an intuitive set of overall, condition-specific, and health system indicators for neonatal care that can be used to track the availability of essential drugs, supplies, and equipment; aggregate readiness loss could be used to compare readiness across health systems, countries, or geographic regions. The low overall readiness among facilities in the cascade study additionally highlights the importance of introducing interventions for small and sick newborns as part of a broader care package. This suggestion is illustrated by a recent study at 24 government hospitals in Malawi that reported improved survival to discharge among neonates weighing 1000-2499g who were treated for respiratory illness after CPAP implementation, but found that 77% of babies with documented admission temperatures were hypothermic and those whose mean temperature was hypothermic during CPAP treatment had reduced survival rates.[131]

8.4. Score to predict mortality amongst hospitalised newborns ≤2000g (NMR-2000)

A variety of scoring systems for predicting mortality risk amongst hospitalised neonates have been developed, primarily for high-resource settings. The NMR-2000 was derived and validated using data from 187 neonatal units in the UK (n=110176) and one hospital in The Gambia (n=550). The final model, which includes three parameters (birthweight, admission SpO_2, highest level of respiratory support within 24h of birth), showed good discrimination in the development and UK validation samples (c-index 0.89) and in the Gambian validation sample (c-index 0.82). Complete scoring data were available for 83% of Gambian neonates. Table 8-1 compares the characteristics and findings of development studies for scoring systems to predict in-hospital mortality amongst admitted neonates.[132–141] Scores developed to predict mortality in neonates who have been transported from another facility (e.g., MINT, TRIPS, TREMS),[142–144] or to enable quality of care comparisons across hospitals, necessitating inclusion of delivery room deaths (e.g., VON-RA),[145] are not presented. As shown in Table 8-1, only one of these scores was designed for use in low-resource settings (SAWS). The SAWS score had moderate discriminatory ability amongst neonates ≤1500g, with c-indices of 0.70-0.71 at the time of derivation and 0.68-0.70 at the time of validation.[132] Importantly, the validation sample for this study was very small (n=39) and solely comprised of neonates from a community-based study in Nepal.[132] A study in Jamaica compared SAWS, CRIB-II, birthweight, and gestational age in a cohort of 109 hospitalised neonates with VLBW and found that birthweight alone was the strongest predictor of mortality ($p<0.01$), with an area under the ROC curve of 0.91 (95% CI: 0.85-0.96).[146] Table 8-1 also

highlights key differences with regard to eligibility criteria, complexity of data collection and scoring, and suitability for use in LMIC settings. NTISS, TRIPS-II, and the various forms of the SNAP score were developed for all NICU admissions; studies of other scoring systems limited enrolment based on birthweight, gestational age, or both. Several systems require a 12 to 24h period for data collection (e.g., CRIB, SNAP-II), while others are not practicable for bedside use due to their length and complexity (e.g., NTISS, SNAP). In contrast to other scores, TRIPS-II and NMR-2000 can be assessed at any point within the first 24h and may be repeated as a baby's clinical condition changes. As discussed in Chapter 4, most of these systems rely on laboratory- and therapy-derived measures (e.g., blood gas) that are typically unavailable or on clinical observations that are not routinely collected or reliably measurable (e.g., urine output) in low-resource neonatal units.[58,65,132] In addition, the NMR-2000 score does not rely on gestational age, which is an advantage relative to the SAWS score given the challenges associated with accurately assessing this measure in LMIC settings (e.g., limited availability of early antenatal ultrasound).[59] Taken together, the findings of this study indicate that the NMR-2000 score is valid for use in health facilities where pulse oximetry is available. These findings also underscore the need to strengthen the quality and coverage of routine health information systems in sub-Saharan Africa. The NMR-2000 score could facilitate individual risk assessment, enabling targeted delivery of care, and has potential to inform neonatal care resource utilisation.

Table 8-1. Scoring systems for predicting in-hospital mortality amongst admitted neonates: Characteristics and findings of development studies

	Medvedev et al[64]	**Gray et al**[133]	**Horbar et al**[134]	**Intl. Neonatal Network**[135]	**Richardson et al**[136,137]	**Maier et al**[138]	**Richardson et al**[139]	**Parry et al**[140]	**Rosenberg et al**[132]	**Lee et al**[141]
Scoring system	NMR-2000	NTISS	NICHHD	CRIB	SNAP, SNAPPE	Unnamed	SNAP-II, SNAPPE-II	CRIB-II	SAWS	TRIPS-II
Study design	Retrospective	Prospective	Retrospective	Retrospective	Prospective	Mixed*	Prospective	Retrospective	Retrospective	Prospective
Year of birth	2010-19	1989-90	1987-89	1988-90	1989-90	1978-87	1996-97	1998-99	1998-2003	2006-08
Geographical location	England and Wales, UK; Banjul, GM	US (locations unspecified)	US (locations unspecified)	UK (locations unspecified)	Boston, US	Berlin, Germany	Canada and US (New England, California)	UK (nationally representative sample)	Bangladesh, Egypt, Nepal†	Canada (15 distinct regions)
Care setting	187 neonatal units (UK), 1 NSCU (GM)	3 teaching hospital NICUs	7 teaching hospital NICUs	4 teaching hospital neonatal units	3 teaching hospital NICUs	1 NICU	17 NICUs in Canada, 13 NICUs in US	54 neonatal units	1 NICU in Cairo, 1 NSCU in Dhaka†	15 tertiary NICUs
Inclusion criteria	BW ≤2000g; not enrolled in eKMC (GM)	Admitted to NICU	BW 501-1500g; inborn	GA <31 weeks or BW ≤1500g	Admitted to NICU	BW <1500g	Admitted to NICU	GA ≤32 weeks	GA ≤33 weeks; BW ≤1500g; age ≤72h	Admitted to NICU
Exclusion criteria	UK datasets: Admitted at >6h of age or post-discharge; stillborn; died in delivery room; moribund	Moribund	None reported	Inevitably lethal congenital anomalies	Died in delivery room; moribund on admission	GA >33 weeks; missing >10% of required data	Died in delivery room; admitted at age >48h or post-discharge; transferred to normal nursery in <24h; moribund	Stillborn; lethal congenital anomaly or metabolic disorder; death due to organ transplant or heart surgery	Congenital malformations; critically ill infants deemed unlikely to survive beyond initial 48h of hospitalisation	Moribund; missing GA at birth
Statistical methods	Reverse step-wise logistic regression, initially including all candidate variables. Assessed discrimination using c-index, goodness-of-fit with Brier score, and calibration using plots of observed vs. predicted mortality risk.	Expert panel reviewed therapy items and assigned weights based on intensity. Assessed association between NTISS and mortality using Mantel Haenzel extension of X^2 test, and goodness-of-fit with H-L.	Reverse stepwise logistic regression, initially including variables associated with death on univariate analyses. Assessed predictive ability using ROC and goodness-of-fit with H-L test.	Reverse stepwise logistic regression, initially including variables associated with death on univariate analyses. Assessed discrimination with ROC and goodness-of-fit with H-L.	Experts selected physiologic items, assigned weights by item severity. Tested SNAP using X^2. Logistic regression including BW, tested variables to select best model (+PE). Assessed discrimination with ROC and goodness-of-fit with H-L test.	Forward stepwise logistic regression to identify variables associated with death. Assessed predictive ability using ROC and goodness-of-fit with H-L test.	Logistic regression, starting with SNAP variables associated with death on univariate analyses. Chose best physiologic model. Perinatal variables then added to select best combined model. Assessed discrimination using ROC and goodness-of-fit with H-L test.	Logistic regression including log-odds of death by BW, sex, and gestation derived from Draper Grid.[147] Candidate variables were then added, with selection of best model using Akaike information criteria.[148]	Categorical GA, weight, and sex variables were combined into SAWS model. Compared predictive ability using ROC of SAWS alone vs. with addition of other candidate variables, then calculated mortality risk for each SAWS category.	Reverse stepwise logistic regression, initially including variables associated with death on univariate analyses. Assessed predictive ability using ROC and goodness-of-fit with H-L test.

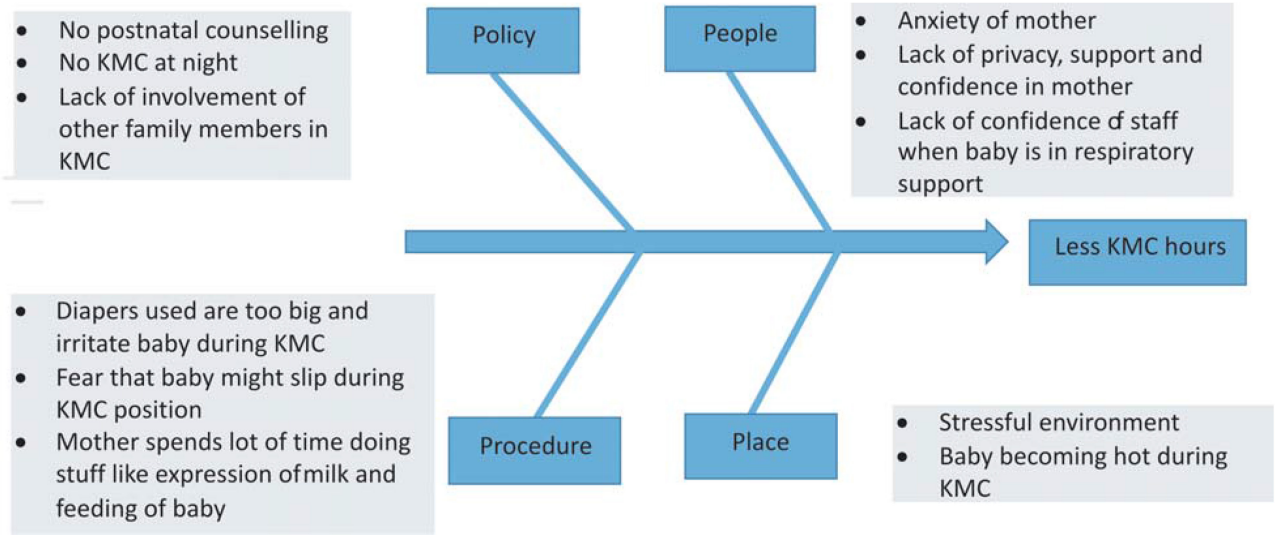
	Medvedev et al[64]	Gray et al[133]	Horbar et al[134]	Intl. Neonatal Network[135]	Richardson et al[136,137]	Maier et al[138]	Richardson et al[139]	Parry et al[140]	Rosenberg et al[132]	Lee et al[141]
Derivation sample size	55029	1768	1823	812	SNAP: 1643 +PE: 1089	396	10819	1886	428†	11383
Validation sample size	55697	NA	1780	488	SNAPPE: 532	176	14610	1065	39†	5692
Deaths in derivation sample, n (%)	1653 (3.0)	114 (6.5)	890 (24.7)‡	201 (24.8)	SNAP: 114 (6.9) +PE: 59 (5.4)	106 (26.8)	418 (3.9)	240 (7.9)‡	262 (61.2)	411 (3.6)
Deaths in validation sample, n (%)	UK: 1701 (3.1) GM: 215 (41.4)	NA	890 (24.7)‡	111 (22.7)	SNAPPE: 33 (6.2)	55 (31.0)	548 (3.8)	240 (7.9)‡	24 (61.5)	199 (3.5)
Parameters in final model (number, type)	1 perinatal, 1 physiologic, 1 therapy	62 therapies	5 perinatal	2 perinatal, 1 diagnosis, 3 physiologic	34 physiologic (SNAP) + 3 perinatal (+PE)	2 perinatal, 1 diagnosis, 1 therapy, 1 physiologic	6 physiologic (SNAP-II) + 3 perinatal (+PE)	3 perinatal, 2 physiologic	3 perinatal	4 physiologic
Timeframe for collection of scoring data	Anytime within 24h of birth	Up to 24h after admission	At time of birth or admission	Up to 12h after admission	Up to 24h after admission	At time of admission	Up to 12h after admission	Up to 1h after admission	At time of birth or admission	Anytime within 24h of admission
Simplified for bedside use?	Yes	No- long and complex tool	No- logistic model only	No- lengthy data collection	No- long and complex tool	Yes	No- lengthy data collection	Yes	Yes	Yes
Suitability for LMIC settings	Yes, if SpO_2 is available	Therapies unavailable	Black race not explanatory	Blood gas, FiO_2 required	Blood gas, OI, FiO_2 required	Blood gas required	Blood gas, FiO_2, UOP required	Blood gas required	Yes, if GA is accurate	Neonatal BP not routine
Discrimination in derivation sample	0.89	X^2: 158.3 p-value: <0.001	0.82	0.92	X^2 p<0.001 (reported only for SNAP)	Not reported	0.91 (reported only for SNAPPE-II)	Not reported	0.70 (GA ≤33 weeks); 0.71 (≤32 weeks)	Not reported
Discrimination in validation sample	UK: 0.89¶ GM: 0.82	NA	0.82	0.90	0.93 (reported only for SNAPPE)	0.86	0.89-0.93§ (reported only for SNAPPE-II)	0·92	0.68 (GA ≤33 weeks); 0.70 (≤32 weeks)	0.87
Goodness-of-fit in derivation sample	0.02	Close agreement	H-L X^2: 14.3 p=0.07#	Not reported	Not reported	p=0.56#	p=0.62# (reported only for SNAPPE-II)	Not reported	Not reported	Not reported
Goodness-of-fit in validation sample	Brier score- UK: 0.03¶ GM: 0.17	NA	H-L X^2: 15.4 p=0.06#	H-L X^2: 16.8 p=0.08#	H-L X^2: 7.5§ p=0.11#&	p=0.99#	p=0.19-0.66§# (reported only for SNAPPE-II)	H-L X^2: 4.3 p=0.83#	Not reported	H-L X^2: 8.3 p=0.14#

NMR-2000=Neonatal Mortality Risk among newborns weighing 2000 grams or less; NTISS= Neonatal Therapeutic Intervention Scoring System; NICHHD=National Institute of Child Health and Human Development; CRIB=Clinical Risk Index for Babies; SNAP= Score for Neonatal Acute Physiology; SNAPPE=SNAP Perinatal Extension; SAWS= Simplified age-weight-sex; TRIPS= Transport Risk Index of Physiologic Stability; GM=Gambia; NSCU=neonatal special care unit; NICU=neonatal intensive care unit; BW=birthweight; eKMC=Early KMC trial; GA=gestational age; ROC=area under receiver operating characteristic curve; H-L=Hosmer-Lemeshow; NA=not applicable; FiO_2=fraction of inspired oxygen; OI=oxygenation index; UOP=urine output; BP= blood pressure. *Data collected retrospectively from 1978 to 1986, and prospectively in 1987. †Derivation sample comprised of hospitalised neonates in Cairo, Egypt and Dhaka, Bangladesh; validation sample comprised of neonates from a community-based study in Sarlahi District, Nepal. ‡Figure represents deaths in the combined derivation and validation samples. ¶Figure represents model performance in the UK full validation sample. §Ranges represent model performance in the Canadian (n=5588), California (n=5530), and New England (n=3492) validation samples. #P-value for Hosmer-Lemeshow statistic (p<0.05 represents poor goodness-of-fit). &Figures represent goodness-of-fit for the SNAPPE score in the combined derivation and validation samples.

8.5. Feasibility study of KMC initiated before stabilisation in Uganda

This study demonstrated that continuous cardiorespiratory monitoring and provision of concurrent therapies were feasible among neonates receiving KMC before stabilisation at Jinja Hospital.[65] Enrolled neonates received an average of four concurrent therapies per day over the first 14 days of admission. A related study in India similarly reported no adverse events (e.g., extubation, loss of venous access) nor significant changes in temperature, respiratory rate, or SpO_2 among LBW infants receiving CPAP (n=15) or mechanical ventilation (n=5) in the KMC position.[149] A recent study in China found that ELBW infants receiving KMC had significantly shorter durations of CPAP (29.5 versus 20.5 days) and nasal intermittent positive pressure ventilation (21.0 versus 13.5 days), relative to infants receiving standard care.[150] In the feasibility study, the median daily duration of KMC ranged from 4.5 to 9.7h. Despite nurse counselling, few neonates received the target duration of 18h per day.[65] An observational study at Jinja Hospital (see Annex A.2) found that the mean daily duration of SSC over the first week of life was 3.0h (SD 2.1) among stabilised newborns weighing 2000g or less; barriers to SSC continuity included maternal illness, lack of privacy, unavailability of chairs for caregivers, and overcrowding in the newborn unit.[151] A RCT of KMC among term infants in Zambia reported that KMC continuity within 24h of birth was negatively affected by postpartum fatigue, maternal illness, routine postpartum checks, and essential newborn care practices.[152] A related study in India identified multiple barriers affecting KMC continuity among hospitalised preterm infants (Figure 8-1).[153] Taken together, these studies emphasise the need for targeted strategies addressing underlying barriers in order to promote KMC uptake and continuity in health facilities.

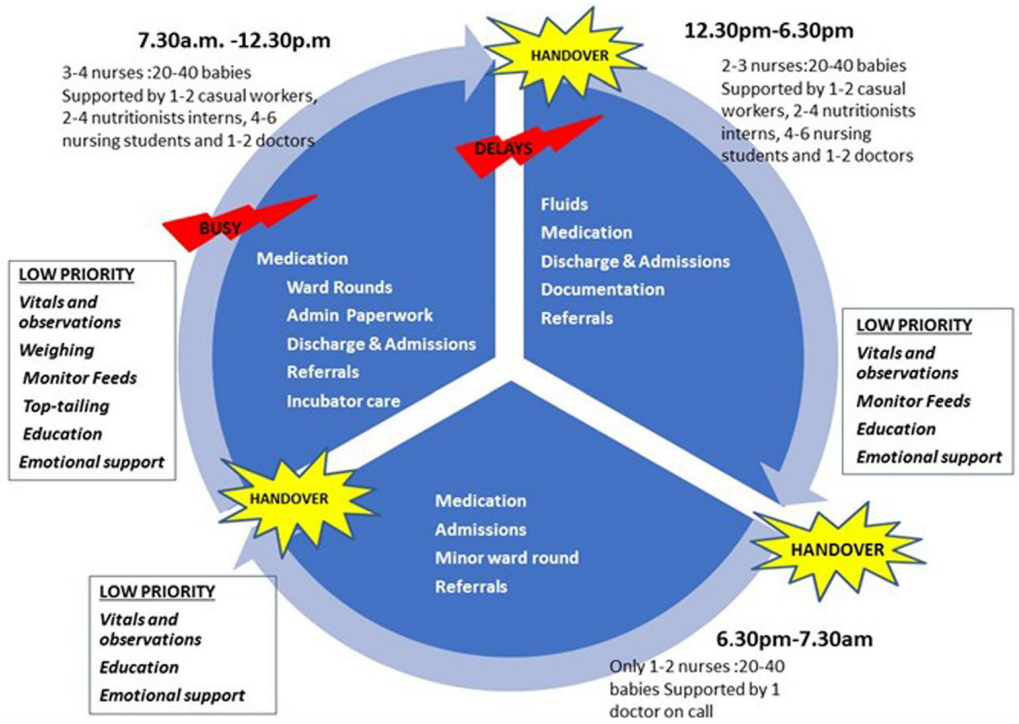
Figure 8-1. Barriers to KMC continuity amongst preterm infants in an Indian NICU



Source: Joshi et al, 2018.[153]

The audit of admissions found that the proposed therapy-based instability criteria were easily implementable. As described in Chapter 5, significant variability exists with regard to how previously published trials of KMC have defined clinical stability.[60,68,70–72,74–76,79,81] These inconsistencies highlight the need for a standardised stability definition as well as uniform criteria for SSC initiation to help health workers determine eligibility for KMC. The qualitative sub-study demonstrated the acceptability of initiating KMC before stabilisation and found that most parents and providers felt monitoring was improved in the KMC position relative to incubator care.[65] Similarly, a study in Zimbabwe reported that mothers felt anxious and helpless when their baby was in an incubator; all mothers preferred KMC because it facilitated close monitoring and on-demand feeding.[154] In Sweden, a related study found that staff in a NICU designed to enable continuous KMC were more comfortable about its use among neonates who were not yet stabilised, including those receiving CPAP or mechanical ventilation.[155] The qualitative sub-study at Jinja Hospital also highlighted challenges related to shortages of staff and monitoring devices, lack of beds and space, insufficient KMC education, and prevalent stigma surrounding preterm birth in local communities.[65] Recommendations to improve KMC practice included staff and peer counselling, family support, and improved availability of beds and monitoring devices.[65] Variable availability of pulse oximetry and scarcities of skilled providers, especially nurses, are critical gaps in LMIC neonatal units.[34–36,156–158] An ethnographic study of neonatal nursing at three Kenyan government hospitals found that standard routines (Figure 8-2) were often interrupted by emergency admissions, care of acutely ill babies, and unanticipated staff shortages; as a result, nurses were habitually burdened with making decisions regarding allocation of inadequate human resources.[159] As shown in Figure 8-2, nurses characteristically prioritised technical tasks (e.g., IV fluids, medications), delegating more basic tasks to student nurses (e.g., vital signs, weighing), mothers (e.g., cup and nasogastric tube feeding), and/or support staff (e.g., bathing and feeding babies, cleaning incubators).[159]

Figure 8-2. Organisation of neonatal nursing work in three Kenyan government hospitals



Source: Nzinga et al, 2019.[159] Tasks in each shift listed in order of nurses' perceived priority. Tasks in adjacent boxes denote lower priority tasks, often delegated to students, mothers, or support staff. Top-tailing=head to toe cleaning.

A related study utilised ergonomics methods to identify the nature and clinical importance of possible errors of nasogastric tube feeding with Kenyan neonatal nursing experts, and found that training and procedural checklists were key strategies for supporting mothers to safely perform this task.[160] Hence, contextually tailored strategies, such as KMC with linked family-integrated neonatal care, are urgently required to address human resource constraints in LMIC settings, e.g., by empowering mothers and caregivers to safely engage in the provision of inpatient care (Figure 8-3).[161–163] In addition, educational outreach programmes in local communities are necessary to address stigma, raise awareness of KMC, and promote social support for mothers and caregivers.

Figure 8-3. Mothers feeding preterm babies by cup and nasogastric tube in Kenya and Afghanistan

Image source: Melissa Medvedev, 2016.

Image source: Médecins San Frontières, 2016.[164]

8.6. Randomised trial of KMC initiated before stabilisation in Uganda (OMWaNA)

The primary aim of the OMWaNA trial is to determine the effect of KMC initiated before stabilisation on early neonatal mortality (within 7 days of birth) relative to standard care at four hospitals in Uganda. In the introductory chapter, I described why the early neonatal period represents a critical window of opportunity to improve neonatal and child survival; estimates suggest that deaths in this timeframe are responsible for 73% of neonatal deaths and 34% of under-5 deaths.[11,20] To date, only one published RCT has examined the impact of KMC on mortality amongst neonates prior to stabilisation relative to standard care.[60] In addition to OMWaNA,[66] three other ongoing RCTs are evaluating the clinical effects of KMC initiated before stabilisation.[82–84] Table 8-2 describes and compares the design of these trials, illustrating several notable discrepancies. These include inconsistencies in outcomes, level of care, stability definition, age at recruitment, and eligibility criteria. The iKMC, eKMC, and OMWaNA trials are investigating the mortality impact of this intervention in East Africa (Tanzania, Uganda); West Africa (Gambia, Ghana, Nigeria); southern Africa (Malawi); and southern Asia (India). These three trials will contribute outcome data on deaths occurring within 72h (iKMC, n=4200), 7 days (OMWaNA, n=2188), and 28 days (iKMC, OMWaNA, eKMC; pooled n=6780) of birth. In contrast, the primary outcome of the IPISTOSS trial is cardiorespiratory stability at 6h of life. The IPISTOSS and iKMC trials are being conducted in hospitals with neonatal intensive care, while the eKMC and OMWaNA trials are taking place in hospitals that provide special care for small and sick newborns. The OMWaNA trial is utilising the same stability criteria as the iKMC trial, while eKMC and IPISTOSS employ distinct stability definitions. The IPISTOSS trial employs gestational age to assess eligibility, while the eKMC, iKMC, and OMWaNA trials use weight. This is likely to be related to the fact that IPISTOSS is being conducted in Scandinavia, where antenatal ultrasonography is widely available. Further, these trials utilise divergent minimum thresholds for weight (e.g., 700g in OMWaNA versus 1000g in iKMC). Notably, some neonates with ELBW do survive with KMC in non-intensive care settings.[26] If the OMWaNA trial suggests mortality reduction in this subgroup, further research will be warranted to assess the impact of KMC in this population in additional LMIC contexts, integrating thoughtful consideration about physical and human resource requirements.

Table 8-2. Randomised controlled trials examining the clinical effects of KMC initiated prior to neonatal stabilisation

	OMWaNA[66]	**Worku et al**[60]	**eKMC**[82]	**iKMC**[83]	**IPISTOSS**[84]
Geographic location(s)	Uganda	Ethiopia	The Gambia	Ghana, India, Malawi, Nigeria, Tanzania	Norway, Sweden
Description of trial hospital(s)	3 regional referral hospitals, 1 district hospital	1 university hospital	1 national referral hospital	5 national referral hospitals	3 university hospitals
Level of care[34]	Special care	Special care	Special care	Intensive care	Intensive care
Trial design	Parallel, two-arm, superiority trial	Parallel, two-arm, superiority trial	Parallel, two-arm, superiority trial	Parallel, two-arm, superiority trial	Parallel, two-arm, superiority trial
Recruitment period	2019-2021	2001-2002	2018-2020	2017-2020	2018-2020
Sample size	Target: 2188 (1094/arm)	Actual: 123 (62 KMC arm, 61 control arm)	Target: 392 (196/arm)	Target: 4200 (2100/arm)	Target: 150 (75/arm)
Definition of clinical stability	SpO_2 >90% (no oxygen); respiratory rate 40-<60*; no apnoea; heart rate 80-179†; temperature 36.0-37.4°C‡; no CPAP or IV fluids	Stable temperature; stable cardiovascular status; satisfactory ability to suck; good general condition	SpO_2 ≥88% (no oxygen); respiratory rate 20-60*; no apnoea; no severe chest in-drawing	SpO_2 >90% (no oxygen); respiratory rate 40-60*; no apnoea; heart rate 80-160†; temperature 36-37.4°C‡; no CPAP or IV fluids	Stability of the Cardio-Respiratory System In Preterms (SCRIP) score;[110] higher score indicates greater physiological stability
Age at recruitment	Within 48h of birth	Mean: 10h (both arms)	Within 24h of birth	Within 2h of birth	Within 1h of birth
Inclusion criteria	Birthweight 700 to ≤2000g; age 1 to <48h; indication for KMC uncertain, defined as receiving ≥1 therapy (oxygen, CPAP, IV fluids, therapeutic antibiotics, phenobarbital); caregiver able and willing to provide KMC and attend follow-up	Birthweight <2000g; no major congenital malformation; singleton unless one twin died; mother healthy and willing to participate	Admission weight <2000g; age 1-24h; availability of study bed; caregiver available and willing to provide KMC	Weight 1000 to <1800g; age 0 to 2h; mother able to provide KMC	Gestational age 28 to <33 weeks; born in maternity ward at study centre; caregiver available to start SSC within 1h of birth
Exclusion criteria	Triplets or more (unless ≥1 triplet died); severely life-threatening instability; severe jaundice requiring immediate treatment; active seizures; major congenital malformation	Not reported	Triplets or more; stable; severely unstable; life-threatening congenital malformation; jaundice requiring treatment; seizures; enrolled in another study	Triplets or more; baby unable to breathe spontaneously within 1h of birth; congenital malformation precluding KMC; mother <15 years, resides outside study area	Outborn; triplets or more; known malformation requiring immediate surgery; known congenital infection; ongoing resuscitation or intensive care (mechanical ventilation or inotropy)

	OMWaNA[66]	Worku et al[60]	eKMC[82]	iKMC[83]	IPISTOSS[84]
Intervention arm	Continuous KMC until discharge (target duration ≥18h/day), with continued KMC at home	Continuous KMC initiated within 24h of birth (duration not reported)	Continuous KMC until discharge (target duration 18h/day), with continued KMC at home	Continuous KMC until discharge (target duration ≥20h/day)	SSC with 1 caregiver continuously during first 6h after birth and as much as possible during first 72h
Control arm	Incubator/radiant warmer until clinically stable, then intermittent KMC (per routine care at study sites)	Radiant heater in heated room until clinically stable, then routine KMC	Incubator/radiant heater until clinically stable, then intermittent or continuous KMC	Separation of mother and baby until baby is clinically stable, then continuous KMC	Incubator/radiant warmer during first 72h after birth
Primary outcome	Mortality within 7 days of birth	In-hospital mortality	Mortality within 28 days of birth	Mortality within 72h, 28 days of birth	Cardiorespiratory stability at 6h of life
Secondary outcomes	Mortality within 28 days of birth; prevalence of hypothermia at 24h of life; time from randomisation to clinical stabilisation; time from randomisation to death; time from randomisation to exclusive breastmilk feeding; duration of hospital admission; frequency of readmission; daily weight gain, infant-caregiver attachment, women's wellbeing at 28 days	Temperature[§]; weight gain[4]; type of feeding[§]; episodes of minor and major illness[§]; episodes of serious illness[§] (diarrhoea, sepsis, pneumonia, aspiration pneumonia); duration of hospital admission; mothers' feelings about method of care	Time from start of intervention/control procedures to death; cardio-respiratory stability (SCRIP score) at 24h; prevalence of hypothermia within 24h; exclusive breastfeeding at discharge; duration of hospital admission; weight gain, incidence of suspected late-onset (>3 days) infection, prevalence of intestinal carriage of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* within 28 days	Incidence of hypothermia, suspected sepsis, probable sepsis, hypoglycaemia; time to stabilisation; time to full breastfeeding; exclusive breastmilk feeding at 28d; maternal satisfaction; maternal depression	Days on respirator, number of surfactant doses, days on CPAP, days on oxygen, number of sepsis episodes, days of antibiotics from birth to discharge; temperature within 6h; breastfeeding status; time to full enteral nutrition; duration of nasogastric tube feeding; time to recovered birth weight; weight gain; epigenetic/telomere profiling in buccal cells/blood; infant EEG maturation; infant structural/functional brain maturation; mother brain responsiveness; mother-infant microbiota, bonding, attunement in regulating stress; parents' experiences; child neuro behaviour

CPAP=continuous positive airway pressure; IV=intravenous; SpO_2=peripheral capillary oxygen saturation; SCRIP=Stability of the Cardiorespiratory System in Preterms; SSC=skin-to-skin contact; EEG=electroencephalogram. *Respiratory rate in breaths per minute. †Heart rate in beats per minute. ‡Axillary temperature in degrees Celsius.
§Outcome measure listed in methods section of manuscript, but not reported.

The OMWaNA trial implementation meeting was held in Entebbe in August 2019. Following completion of neonatal unit renovations and an initial pilot phase, the trial commenced official recruitment in January 2020. An economic evaluation embedded within the trial will compare the incremental cost and cost-effectiveness of KMC relative to standard care from the societal perspective. Findings of the economic evaluation could help guide allocation of resources for newborn care and potential strategies to address opportunity costs for families. The accompanying process evaluation will explore hypothesised causal pathways for the clinical effects of KMC initiated before stabilisation and examine barriers and facilitators to inform the uptake and sustainability of this intervention in Uganda and related contexts, if shown to be effective. The process evaluation will include triannual surveys of staff, supply, medication, and equipment availability as well as biannual neonatal quality of care surveys, including progress monitoring of KMC services. As KMC provision in Ugandan health facilities is not routinely recorded, the process evaluation may have important implications regarding the need for a standardised system to track national coverage and quality of KMC services. Improved understanding of potential underlying mechanisms, including brain injury following preterm birth, could inform programmes and interventions to help prevent disability and related downstream effects on human capital and wellbeing, in line with the post-2015 SDG agenda.[18]

8.7. Strengths and limitations of this PhD

8.7.1. Strengths

An important strength of this PhD is the utilisation of primary data collected from sub-Saharan Africa to evaluate three objectives (facility assessment data from Kenya and Uganda, the risk score validation data from The Gambia, and the feasibility study data from Uganda), which together informed design of the OMWaNA trial in Uganda (Table 8-3).

Table 8-3. Informing the design of the OMWaNA trial using mixed methods

	Study finding(s)	Impact on trial design
Chapter 3 (clinical cascades to assess facility readiness for neonatal care)	Among the 23 Kenyan and Ugandan facilities, the model estimated overall readiness of 27% in 2016 and 26% in 2017; mean readiness by cascade ranged from 12% (respiratory distress-apnoea) to 48% (essential newborn care) across both time-points	Site staff completed training on standardised clinical guidelines (including signs of severe illness), pulse oximetry monitoring, KMC, and Ballard scoring prior to start of the trial, plus ongoing refresher training on guidelines and KMC
	Across 23 Kenyan and Ugandan health facilities, 22-44% had a functional pulse oximeter with neonatal probe, 26-30% had KMC beds or chairs, and 4-35% had a functional glucometer	Provision of 6 Masimo Rad-8© pulse oximeters with neonatal probes, 4-5 adjustable KMC beds, and 1 glucometer with blood glucose testing strips at each site
	Variability in the timing of readiness loss, with increased loss in treatment stage for essential newborn care, poor feeding-hypothermia, and infection-convulsion cascades in 2017 vs. 2016	Process evaluation will assess changes in care between hospitals and from before trial, including baseline and triannual surveys of staffing, supplies, and equipment
Chapter 4 (NMR-2000 risk score development and validation)	NMR-2000 is a validated mortality score for hospitalised neonates ≤2000g in settings where pulse oximetry is available; NMR-2000 demonstrated good discrimination, goodness-of-fit, and calibration across the UK and Gambian external validation samples	Data needed for score calculation are collected as part of the trial; subgroup analysis will explore between-group difference in the impact of KMC vs. standard care on mortality, by level of predicted risk based on NMR-2000 score
	As the Gambian sample was small and limited to a single site, NMR-2000 requires further validation using a larger dataset from LMIC settings	Follow-up validation study using pooled data from the OMWaNA trial and a large, multi-hospital study in Kenya is planned
Chapter 6 (KMC feasibility study at Jinja Hospital)	Audit found that the instability criteria were easily implementable; among neonates who received only 1 therapy, majority received empiric antibiotics because they were at risk of infection	Instability criteria were modified to 1 or more therapies, excluding empiric antibiotics, for the trial
	Audit estimated ≥400 eligible neonatal admissions per year at Jinja Hospital	Estimate informed sample size calculations for the trial

Table 8-3 continues on the following page.

	Study finding(s)	Impact on trial design
Chapter 6 (KMC feasibility study at Jinja Hospital)	Continuous monitoring of heart rate and SpO_2 was feasible among neonates in the KMC position	All neonates receive continuous monitoring of heart rate and SpO_2 for 72 hours; monitoring continues until participants no longer require any form of respiratory support
	Qualitative sub-study identified staffing shortages in the neonatal unit as a key barrier to KMC practice	One study medical officer and 4-5 nurses were recruited at each site; process evaluation comprises triannual staffing and biannual quality of care surveys, including progress monitoring of KMC provision/services (Annex A.9)
	Qualitative sub-study identified shortages of monitoring devices, beds and space; insufficient KMC education; and stigma surrounding preterm birth in local communities as key barriers to KMC practice	Staff and peer counselling on KMC and care of preterm/LBW neonates; substantial infrastructure improvements in newborn units (increased space, sinks, bathrooms for caregivers); provision of pulse oximeters, beds, and KMC wraps

By employing mixed methods, including collection of both quantitative and qualitative data, this work facilitated a greater understanding of the barriers and facilitators affecting KMC provision and inpatient care amongst small and sick newborns before stabilisation in these sub-Saharan African contexts. Given the involvement of a highly vulnerable population, this detailed level of understanding was invaluable during the process of preparing a successful funding application for the Joint Global Health Trials scheme, developing the trial protocol, and planning and implementing the trial across the four Ugandan government hospitals. In particular, these findings underscored the need for substantial infrastructure improvements within the neonatal units in advance of trial commencement and comprehensive capacity building. Another strength is that the NMR-2000 study represents the largest dataset utilised to develop and validate a neonatal mortality risk score (Table 8-1). In addition, to our knowledge, the NMR-2000 is the only score for predicting in-hospital neonatal mortality that has been validated in a low-resource (i.e., non-intensive care) facility setting.

8.7.2. Limitations

The main overall limitation of this PhD is the small size of the sub-Saharan African samples utilised in the studies that informed the design of the trial, since the Gambian validation and Ugandan feasibility studies were each limited to a single hospital. Further research is required to validate the NMR-2000 score in LMIC settings using larger, multi-site datasets. Similarly, the

cascade study assessed 23 facilities within two regions of East Africa; thus, future work is needed to evaluate this model in different geographic and cultural contexts. The feasibility audit and the NMR-2000 study were both limited by the presence of missing data in routine hospital records. Several studies have described issues regarding collection of data on neonatal inpatient care in LMICs,[65,157,165] underscoring the fact that effective implementation of the NMR-2000 score in such settings would require sensitisation among health workers. As demonstrated by the findings of the cascade study and related studies in sub-Saharan Africa,[63,156–158] the usefulness of the NMR-2000 score could be limited by variable availability of pulse oximetry in low-resource neonatal units. The cascade model assesses the physical readiness of facilities; however, it does not evaluate knowledge or skills among newborn care providers. A study at 11 Ethiopian facilities reported that providers performed 62% and 57% of the recommended tasks of immediate and postnatal newborn care, respectively,[166] while a multi-country African study showed that neonatal asphyxia was correctly diagnosed by fewer than half of providers.[167] In Tanzania, a Helping Babies Breathe programme evaluation found that the proportion of providers passing the clinical examination declined from 87% immediately after training to 56% at 4-6 months.[168] These studies emphasise the critical importance of routinely assessing provider knowledge and skills alongside regular monitoring of physical and human resource availability across levels of the health system.

Other important limitations relate to challenges that have been identified during the design and implementation of the OMWaNA trial. The involvement of small and sick newborns before stabilisation, together with the fact that a caregiver must be available to provide KMC within 48h of birth, could present difficulties in obtaining timely and valid informed consent. Parental capacity to give valid consent may be affected by emotional state and level of understanding, as well as by the time available to process the information and make a decision.[169–172] Adherence to near-continuous KMC may be challenging for a variety of reasons, such as maternal illness, lack of privacy, and insufficient family or social support.[65,67,151–153] Intervention adherence could also be diminished by parents or caregivers witnessing a death, especially one occurring in the KMC position.[161] As some degree of non-adherence is unavoidable, the potential for resultant dilution of the effect size of KMC was taken into account during the sample size calculations. Finally, although substantial efforts were undertaken to improve neonatal care capacity, government hospitals in Uganda often experience human resource constraints, drug and supply shortages,[34,63] delayed repair of equipment, and periodic interruptions to the electrical supply,[158,173] which is necessary to power radiant warmers, incubators, oxygen concentrators, and phototherapy.

9. Recommendations and conclusion

9.1. Scope of this chapter

This PhD has developed a cascade model to evaluate facility readiness, validated a score to assess individual risk and guide resource provision, and demonstrated the feasibility of initiating KMC before stabilisation. These studies have informed the design of a RCT that will determine the mortality impact of this intervention relative to standard care, resulting in development of the protocol for an ongoing four-centre trial in Uganda. In this final chapter, I use the findings of this PhD to provide recommendations for policy, programmes, and future research.

9.2. Recommendations for policy and programmes

In line with current WHO guidelines, recommendations for policy and programmes pertain to facility-initiated KMC among stable neonates, except where otherwise noted. If evidence from ongoing trials demonstrates the effectiveness of KMC among neonates prior to stabilisation, these recommendations could also be applied to KMC practice in this population.

Table 9-1. Summary of recommendations for policy and programmes

	Actions for policy and programmes
Individual/household-level (babies, mothers, families, local communities)	Operationalise strategies in health facilities to promote KMC uptake and continuity throughout hospitalisation and at home after discharge
	Engage peer counsellors and local champions to support KMC practice including at home after discharge
	As part of Universal Health Coverage and financial protection, address opportunity costs for families, particularly those of neonates requiring prolonged hospitalisation
	Raise awareness about KMC, enhance social support for caregivers, and address stigma surrounding preterm birth in local communities
Health system-level (facilities, administrators, care providers)	Employ individual risk assessment in routine care to inform planning
	Estimate the budget impact of KMC relative to standard care to inform allocation of resources for neonatal care across levels of the health system
	Develop, implement, and monitor comprehensive newborn care packages, including space, health workers, and essential devices and equipment (e.g., NEST360°)
	Implement family-integrated neonatal care in health facilities, contextualising evidence from other settings

Table 9-1 continues on the following page.

	Actions for policy and programmes
National-level (e.g., Uganda Ministry of Health, Uganda Paediatric Association)	Promote national scale-up of inpatient care for small and sick newborns, including KMC
	Introduce national system for routine monitoring of KMC provision and services in health facilities
	Strengthen routine health information systems, integrating collection of neonatal inpatient data across levels of care
	Enhance supply chain management systems, incorporating cascade-derived indicators to track the availability of supplies and equipment
International-level (e.g., WHO, UNICEF)	Establish consensus regarding standardised criteria for KMC initiation, incorporating a clear and uniform definition of clinical stability
	Develop evidence-based guidelines on building suitable environments for KMC provision across levels of neonatal care
	Promote KMC implementation and scale-up in all countries
	Take actions to further scientific understanding of underlying pathways for the clinical effects of KMC initiated before stabilisation

9.2.1. Individual/household-level

9.2.1.1. Promotion of KMC uptake and continuity in facilities

To promote KMC uptake and continuity throughout hospitalisation and at home after discharge, targeted strategies should be employed within facilities across the healthcare system. Sensitisation efforts should be conducted in antenatal clinics and maternity wards to raise awareness about KMC. Numerous studies have demonstrated the importance of positive perceptions among parents and families regarding the benefits of KMC to both babies and caregivers.[174–176] Healthcare workers should clearly explain and discuss these benefits with parents, families, and other involved individuals,[175] taking time to thoughtfully address their questions and concerns. An Indian study found that a KMC improvement initiative, including comprehensive counselling for families, weekly nurse champions, emphasis of SSC duration in the daily treatment order, and unlimited visitation for family members, increased the mean daily duration of SSC from 3h to 6h over a 7-week period.[153] Evaluations at 6 and 12 months post-implementation suggested sustained improvements in SSC duration of up to 9h per day.[153] A related study in the US reported that a KMC pathway, integrated within a training program comprised of clinical champions (e.g., nurses, respiratory therapists) and a simulated educational video for NICU staff and parents, increased the frequency of SSC 2.4-fold overall and 1.8-fold among neonates receiving invasive respiratory support.[177]

9.2.1.2. Peer counsellors and KMC champions

In LMIC settings, where awareness of KMC and preterm birth are generally low, health workers and caregivers may be engaged to share success stories about small and vulnerable babies who received KMC and survived.[174,175] In the acceptability study at Jinja Hospital, parents and newborn unit providers agreed that peer counselling is a valuable tool for supporting KMC practice.[65] Studies in Malawi, Mozambique, and South Africa also found that new mothers had positive perceptions of learning about KMC from peers who had personal experience.[178–180] In line with the suggestion of a provider at Jinja Hospital,[65] nurses in Mozambique felt that follow-up visits were an opportunity for mothers who had practiced KMC to share their experiences.[178] Further, Malawian mothers who had KMC experience were enthusiastic about acting as KMC champions in the future.[179]

9.2.1.3. Programmes to address opportunity costs for families

Targeted programmes are also needed to reduce the financial burden and address opportunity costs for families, particularly those of neonates who require prolonged hospitalisation. Potential barriers to KMC continuity include competing work and household responsibilities, including care of other children,[175,176,181,182] and transport time and costs.[175,176,182] Approaches to address these issues may include transportation vouchers; unlimited visitation hours; home follow-up visits by trained nurses or community health workers; directed financial assistance; and financing schemes to help reduce out-of-pocket expenses.[161,175,176] For example, Colombia offers public and private health insurance plans covering all costs for LBW babies receiving KMC, including follow-up though 12 months corrected-age.[161] In LMICs that lack universal insurance coverage, community-based or mutual health insurance is an alternative funding mechanism. A population-wide study in Rwanda found that mutual health insurance was associated with reduced household financial burden as well as increased utilisation of healthcare services.[183]

9.2.1.4. Initiatives to raise awareness of KMC, promote social support, and address stigma

Perceptions of fatalism and stigma around having a preterm baby are prevalent in LMIC settings.[178,179,184,185] Societal and cultural norms may dictate that fathers should not play a major role in newborn or child care.[67,176,179] A study in South Africa found some fathers felt uncomfortable learning about KMC from anyone other than their partner,[186] while one in Brazil reported that some mothers and traditional birth attendants felt uncomfortable when fathers practiced KMC.[187] Community-based programmes may be leveraged to raise awareness about

KMC, enhance social support for caregivers, and address stigma regarding preterm birth. Such efforts could include provision of information about KMC through print media, drama, or discussions on radio or television; promotion of activities to celebrate a baby's graduation from KMC; and peer- and elder-led community education programmes;[154,175,188] as well as context-specific programmes to encourage paternal involvement in KMC and newborn care.[189] For example, the Ekendeni Agogo Programme in Malawi trained 4100 respected grandparents to educate new and expectant mothers and their families about maternal and newborn care practices through group and individual counselling, using songs, poems, and drama to convey key messages.[190] Training included an overview of KMC and its benefits; demonstration of the KMC position; and discussion about the role of family members in supporting KMC.[191] An evaluation of the programme reported increased facility-based care seeking and exclusive breastfeeding, and reduced use of harmful traditional practices.[190] In a related study, community leaders in Malawi identified several key actions to address stigma and raise awareness about KMC. These included promoting counselling among families of preterm infants; instituting public meetings to discuss preterm birth and KMC; and creating local leadership networks focused on these issues.[179]

9.2.2. Health system-level

9.2.2.1. Clinical monitoring and care provision, informed by individual risk assessment

Enabling clinical monitoring and care of neonates in the KMC position is critical. The feasibility study demonstrated that cardiorespiratory monitoring and therapy provision were practicable in the KMC position, but highlighted challenges related to shortages of monitoring devices and healthcare providers.[65] The cascade study similarly found that more than half of the facilities did not have a functional pulse oximeter and neonatal probe at both timepoints. In line with these findings, numerous studies have reported that LMIC facilities frequently lack sufficient nurses or pulse oximeters to enable continuous monitoring of all neonates receiving supplemental oxygen therapy.[158,192–195] Studies in The Gambia, Kenya, and Nigeria have reported that hypoxaemia on neonatal admission increased the odds of mortality by three-fold to eight-fold.[156,196,197] Thus, inconsistent availability of routine pulse oximetry in neonatal units is a crucial gap that must be addressed. Assessment of individual risk using the NMR-2000 score could inform neonatal care delivery planning,[33] and support shared decision-making among providers.[198] Further, the NMR-2000 may help expedite recognition of severe illness and enable targeted provision of interventions to help promote neonatal survival.[18,26,199]

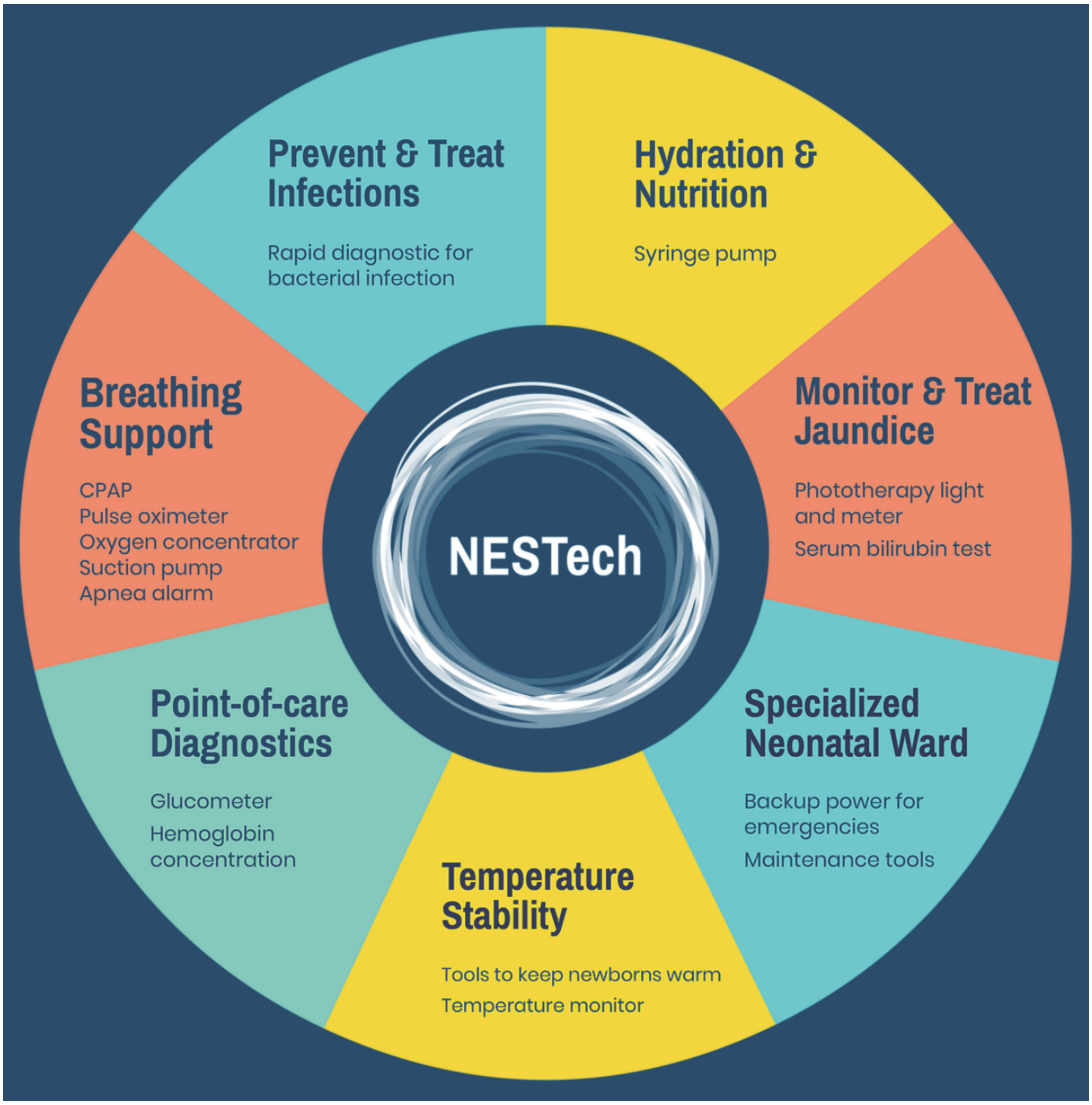
9.2.2.2. Estimating the budget impact of KMC relative to standard care to inform allocation of resources for neonatal care

Incubators are currently the standard of care for maintaining normothermia in preterm and LBW neonates prior to stabilisation. Costs associated with incubators include purchase price, electricity requirements, and maintenance for mechanical dysfunction. Medical costs may arise as a result of nosocomial infections, particularly in neonatal units with ineffective cleaning standards or where incubators are shared,[48,52] a common practice in low-resource settings.[45] The OMWaNA trial will estimate the budget impact of KMC relative to standard care, which could help guide decision-making and inform allocation of resources for neonatal care across levels of the health system. Further, estimation of running costs may inform planning at individual health facilities.

9.2.2.3. Comprehensive newborn care packages, including space, health workers, and essential devices and equipment

In LMICs, an urgent need remains to scale-up effective interventions targeting the major causes of neonatal mortality and morbidity. Findings of the cascade study and the aforementioned study of CPAP implementation in Malawi have underscored the value of introducing interventions for small and sick newborns as part of a broader care package.[63,131] One example of such an approach is NEST360° (Newborn Essential Solutions and Technologies), an initiative that is developing and implementing a comprehensive newborn care package in hospitals across Kenya, Malawi, Nigeria, and Tanzania, with an overarching aim to reduce neonatal mortality in sub-Saharan African hospitals by 50%.[200] NEST360° is employing a strategy that addresses four key gaps in neonatal care by: 1) optimising a bundle of rugged and affordable technologies (Figure 9-1), with ongoing support and maintenance; 2) training clinicians and biomedical engineers on technology implementation and innovation; 3) collecting data to improve quality of care and facilitate wider adoption; and 4) developing a market to enable sustainable distribution of devices and equipment to health systems across Africa.[200]

Figure 9-1. NEST360° (Newborn Essential Solutions and Technologies)



Source: Rice360°, 2019.[200]

9.2.2.4. Family-integrated care

As described in Chapter 8, family-integrated care (FIC) represents a potential approach to help address human resource shortages in LMIC neonatal units. The aims of FIC are to promote parent competence and confidence, enhance family well-being, and improve infant health outcomes at the time of hospital discharge.[162] The core components of FIC include family-centred neonatal unit design and policies (e.g., family spaces, unlimited visitation); staff training on how to teach parents to safely provide neonatal care; parent psychoeducational support (e.g., group classes, nurse and/or peer mentorship); delivery of neonatal care by parents as much as able (targeting ≥6h per day); and frequent provider-parent communication with shared decision-making.[162,201–204] A cluster RCT in 25 NICUs across Canada, Australia, and New Zealand found that FIC for preterm neonates resulted in improved infant weight gain at day 21, decreased parental stress and anxiety

at day 21, and increased breastmilk feeding incidence at discharge relative to standard care.[163] A study of a FIC intervention bundle including a parent support mobile application in two UK neonatal units showed that, relative to historical controls, preterm infants who received FIC were discharged earlier (corrected gestational age 36 versus 37 weeks), had reduced overall LOS, and reached full enteral and full suck feeds earlier.[205] A pre-post FIC intervention study in two Chinese NICUs found that infants who received FIC had increased breastfeeding incidence, breastfeeding duration, enteral nutrition duration and weight gain, and reduced duration of respiratory support relative to controls.[206] A follow-up study reported that FIC infants scored higher on the Bayley Mental and Psychomotor Developmental Indices at 18 months of age.[207] Although studies are needed to assess its impact in LMIC contexts, existing evidence suggests that practicing KMC and linked family-integrated neonatal care could empower mothers and families, reduce nursing workload, promote earlier discharge, and improve newborn survival.

9.2.3. National-level

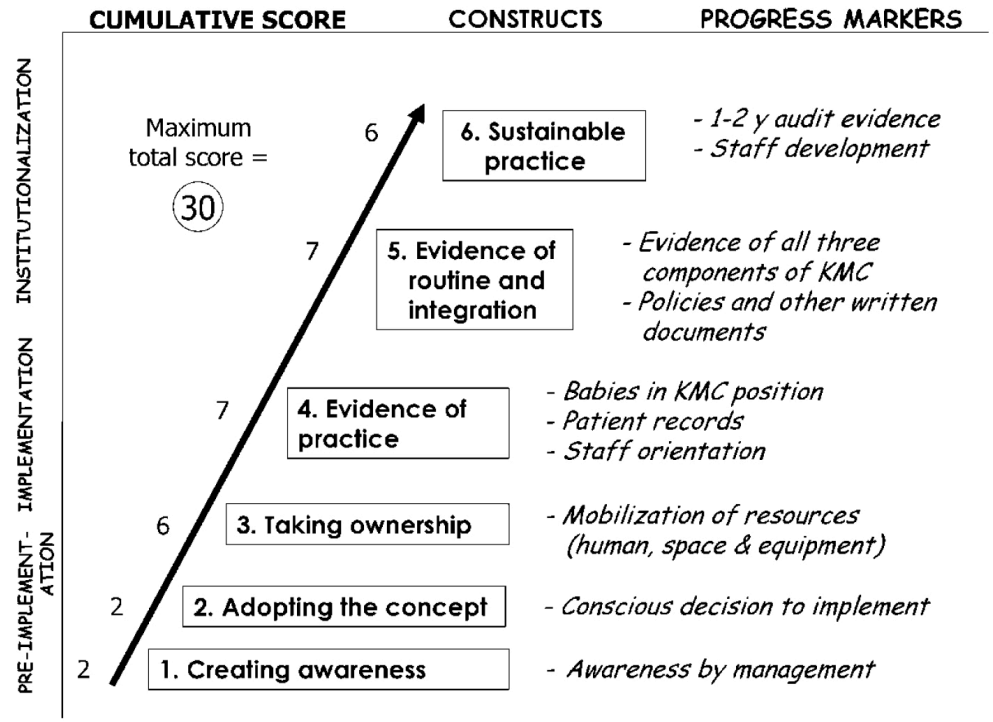
9.2.3.1. National scale-up of KMC in health facilities

In 2006, the Ugandan Ministry of Health established a Newborn Steering Committee, which advised scale-up of KMC for stable neonates.[208] KMC has now been implemented in all Ugandan district hospitals; however, further efforts will be required to achieve national coverage in all facilities. Studies in South Africa have demonstrated that KMC can be successfully implemented in facilities by introducing a multimedia training package in combination with group facilitation sessions, either on-site or at a centre of excellence, highlighting the importance of administrative support and endorsement by local opinion leaders.[209,210] Establishing regional, district, and institutional KMC steering committees was a key component of a successful implementation initiative at 38 hospitals in Ghana.[211] These committees convened regularly to monitor progress, plan activities, and discuss issues affecting project execution.[211] Several countries in sub-Saharan Africa and southern Asia have engaged neonatologists, paediatricians, and related professionals as champions to advocate for KMC.[161,212–215] In Uganda, the Ministry of Health's Newborn Steering Committee and the Uganda Paediatric Association should be involved throughout the scale-up process. Further, neonatal and maternal health experts from these organisations could facilitate identification of suitable individuals to serve as national or regional KMC champions.

9.2.3.2. National system for routine monitoring of KMC provision and services in facilities

Efforts should be made to establish a countrywide system for routine monitoring of KMC provision and services in health facilities. Key stakeholders in Uganda have recognised the scarcity of KMC coverage data within the existing health information system as a major barrier to scale-up efforts.[161] Bergh et al developed a KMC assessment instrument based on a staged model of progress monitoring that includes three phases (pre-implementation, implementation, institutionalisation), beginning with creation of awareness and culminating in sustainable practice (Figure 9-2).[216] This comprehensive tool (Annex A.9) is being utilised to monitor KMC provision and services biannually across the four sites as part of the OMWaNA process evaluation.

Figure 9-2. KMC progress monitoring model



Source: Bergh et al, 2005.[216]

9.2.3.3. Improved quality and coverage of routine health information systems

Enhancing the quality and coverage of routine health information systems is critical to promote actions to improve neonatal survival.[157,217] This will require coordinated efforts across levels of the health system, including post-discharge follow-up care. Particular attention should be directed to improving the capacity of these systems to collect inpatient data on babies who die shortly after birth or are transferred to another facility,[23] as well as longer-term follow-up data on preterm and VLBW babies who face an elevated risk of neurodevelopmental impairment in childhood.[218–220]

9.2.3.4. Strengthening of existing supply chain management systems

Strengthening of existing healthcare supply chain management systems should also be prioritised, including incorporation of cascade-derived indicators to monitor facility readiness and track the availability of essential drugs, supplies, and equipment. A multi-country analysis of bottlenecks affecting neonatal inpatient care highlighted the fact that inadequate and imprecise logistics systems often limit the capacity of health systems to predict demand for oxygen, supplies, and equipment maintenance in facilities.[34] Stakeholders in sub-Saharan Africa and southern Asia have reported limited availability of special care equipment, including CPAP systems, and frequent shortages of key commodities, including cannulas, antibiotics, and preterm feeding supplies.[34,161] The cascade study similarly revealed low availability of CPAP, nasal cannulas, nasogastric tubes, and certain antibiotics; additionally noting that IV bags and tubing, glucose test strips, KMC beds and chairs, and functional phototherapy devices were available in fewer than one-third of the facilities.[63] The cascade model provides a set of indicators for neonatal inpatient care that can be used to evaluate individual facilities and compare readiness estimates across health systems, countries, or geographic regions.[63,221] Further, by precisely identifying the timing and location of readiness loss, the cascade model could help guide resource allocation decisions and facilitate improved quality of care for small and sick newborns.[199]

9.2.4. International-level

9.2.4.1. Standardised criteria for KMC initiation, including clear definition of stability

A key priority at the international-level is to establish consensus regarding standardised criteria for KMC initiation. These criteria should incorporate a clear and uniform definition of clinical stability. This process should take into consideration the findings of ongoing trials, including eKMC, iKMC, IPISTOSS, and OMWaNA. Taking these actions to harmonise guidance would support clinical decision-making by enabling care providers to more consistently and objectively determine which newborns are stable enough to safely receive KMC.

9.2.4.2. Guidelines on suitable environments for KMC provision across levels of care

Policymakers and technical agencies should also prioritise the development of harmonised guidelines on building suitable environments for KMC practice at each level of neonatal care. These guidelines may include provision of beds, chairs, and KMC wraps, as well as infrastructure improvements (e.g., sinks, toilets, private space for caregivers).[176,222] Clinical monitoring devices,

such as pulse oximeters, may additionally be advised for facilities that provide ongoing care to small and sick newborns (i.e., special and intensive neonatal care). Incorporation of estimated financing requirements by level of care across different geographic regions could help facilitate wider adoption and implementation of such guidelines.

9.2.4.3. Implementation and scale-up of facility-initiated KMC in all countries

The United Nations Children's Fund (UNICEF) is committed to wider implementation of newborn care in priority countries, including Uganda, and has highlighted KMC as a key intervention.[223] The ENAP has prioritised KMC implementation across all levels of the health system.[19] A recent WHO report estimated that KMC could save nearly 70,000 newborn lives in 81 high-burden countries in 2025, if 95% of facility deliveries have access to comprehensive EmONC and newborn special care.[39] The International Network on KMC was established to support programme implementation, promote knowledge sharing, and provide training to healthcare institutions, professional associations, and governmental and non-governmental agencies.[224] Together, these stakeholders can help facilitate widespread and effective scale-up of KMC in facilities, including KMC initiated before stabilisation (if proven to be effective).

9.2.4.4. Scientific understanding of causal pathways for beneficial effects of KMC

Key stakeholders, policymakers, and technical agencies should also prioritise actions to advance scientific understanding regarding potential causal pathways for the beneficial clinical effects of KMC, including KMC before stabilisation. Heightened understanding of underlying mechanisms for these effects could inform specific approaches to improve inpatient care and health outcomes for small and sick neonates. Further, such knowledge could guide innovative strategies to help prevent early childhood disability, empowering these vulnerable babies to survive and thrive.

9.3. Implications for research

Table 9-2. Summary of implications for future research

	Research questions to address remaining evidence gaps
Description	Determine minimum dose per 24h required to achieve beneficial effects on neonatal survival and other important clinical outcomes, or potential threshold for time in intermittent KMC
	Long-term follow-up to assess neurodevelopmental outcomes and early childhood disability after KMC, adjusting for gestational age
	Follow-up to evaluate the effects of KMC on mental health and wellbeing among both mothers and babies
Discovery	Further explore underlying physiological mechanisms by which KMC may affect clinical outcomes, including KMC initiated prior to stabilisation
	Develop cheap and robust devices to accurately capture and record time spent in the KMC position
	Develop cost-effective approaches for retinopathy screening and treatment in LMIC settings, incorporating contextually-appropriate screening criteria
Delivery	Validate and integrate indicators to track KMC coverage and quality through routine health management information systems
	Further validate the NMR-2000 score in LMIC settings and explore its utility to support clinical decision-making and inform resource utilisation, including nursing workload
	Compare the clinical cascade model with other facility readiness assessment tools, and explore the association between aggregate readiness loss and neonatal mortality
	Evaluate the incremental cost and cost-effectiveness of KMC, including additional costs of KMC initiated before stabilisation, relative to standard care from the societal perspective, considering impact on women and households, in other LMIC contexts

9.3.1. Description

9.3.1.1. Minimum dose required to achieve beneficial clinical effects of KMC

The most recent WHO guidelines for preterm care highlighted the lack of evidence regarding the dose-response relationship between KMC duration and mortality reduction as a key research priority.[12] Hence, research is needed to determine the minimum dose of continuous KMC per 24h that is required to achieve beneficial effects on neonatal survival and other important clinical outcomes. Future research should also evaluate the potential threshold for time in intermittent KMC that may be needed to attain positive impacts on newborn health.

9.3.1.2. Impact of KMC on early childhood disability and neurodevelopmental outcomes

Further research is required to advance scientific understanding concerning the effects of KMC on early childhood disability and neurodevelopmental outcomes, including cognitive, motor, language, social, and emotional skills and capabilities. Several studies have suggested that KMC is associated with improved cognitive development. A case-control study in Israel found that infants who received KMC had improved cognitive development at 6 months of age, scoring higher on the Bayley Mental and Psychomotor Developmental Indices relative to controls.[225] A later study by the same group found that infants who received KMC scored higher on the Bayley Mental Developmental Index at 6, 12, and 24 months, and had better executive functioning at 5 and 10 years of age.[102] Evidence from high-income settings has demonstrated the beneficial effects of family-centred developmental care, including cue-based caregiving and KMC, on cognitive and behavioural outcomes in preterm and VLBW babies.[226–229] A 20-year follow-up study of former LBW infants in Colombia who participated in a KMC trial demonstrated that KMC had long-lasting social and behavioural protective effects.[90] These included reduced school absenteeism and decreased hyperactivity, aggressiveness, and socio-deviant conduct as young adults.[90] Further long-term studies are needed to assess the effects of KMC on early childhood disability and neurodevelopmental outcomes through adolescence, especially in sub-Saharan Africa and southern Asia where evidence is scarce.

9.3.1.3. Long-term impact of KMC on mental health and wellbeing in mothers and babies

Preterm babies exhibit heightened stress as a result of increased HPA reactivity together with exposure to stressful environments, painful procedures, and maternal separation.[107–109] Mothers of preterm babies experience higher levels of stress and mental health issues, including a two- to three-fold increased risk of postpartum depression relative to mothers of term babies.[230] Further, several studies in high-income settings have reported that postpartum depression and maternal stress negatively impact neurocognitive outcomes among children born preterm.[231–234] Several studies have suggested that KMC may improve mental health and wellbeing outcomes, including postpartum depression;[225,235–237] maternal anxiety;[102,236,238] mother-infant stress;[102,107–109,239,240] and mother-infant attachment.[74,102,225,239,241] A recent meta-analysis demonstrated that KMC was associated with a 1% reduction in standardised postpartum depression scores among mothers of preterm or LBW neonates relative to standard care; however, high heterogeneity existed among the eight included studies.[242] Hence there remains a need for additional research, including long-term follow-up studies, to improve understanding regarding the effects of KMC on mental health, stress, and wellbeing among both mothers and infants.

9.3.2. Discovery

9.3.2.1. Exploration of underlying physiological mechanisms for the clinical effects of KMC

Further research is needed to explore the underlying physiological pathways by which KMC may affect clinical outcomes, including KMC initiated before stabilisation. Potential mechanisms include improved thermal control;[49,69,70,77,81,85] reduced risk of IVH and late intracerebral sequalae of prematurity;[87] accelerated brain maturation and neurophysiologic organisation;[89,90,99–102] enhanced cardiorespiratory stability;[50,103–106] attenuated HPA response to stress;[107–109] increased breastmilk production;[115,116] and augmented microbiome maturation.[117–120] The OMWaNA trial will further understanding regarding the effects of KMC on thermal control and prevalence of IVH and late intracerebral sequelae of prematurity,[66] while the IPISTOSS trial will provide valuable data on infant EEG and brain maturation, mother-infant stress attenuation, and mother-infant microbiota (Table 8-2).[84] All four ongoing trials are evaluating impact on cardiorespiratory stability, with eKMC and IPISTOSS using the SCRIP score,[110] and iKMC and OMWaNA using the WHO's stability definition.[83] The eKMC trial will also contribute novel data regarding the infection prevention effects of KMC by conducting microbiological tests for suspected infections and examining impact on intestinal carriage of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*,[82] a major cause of invasive neonatal infections in sub-Saharan Africa.[243]

9.3.2.2. Cheap and robust devices to accurately capture and record time in the KMC position

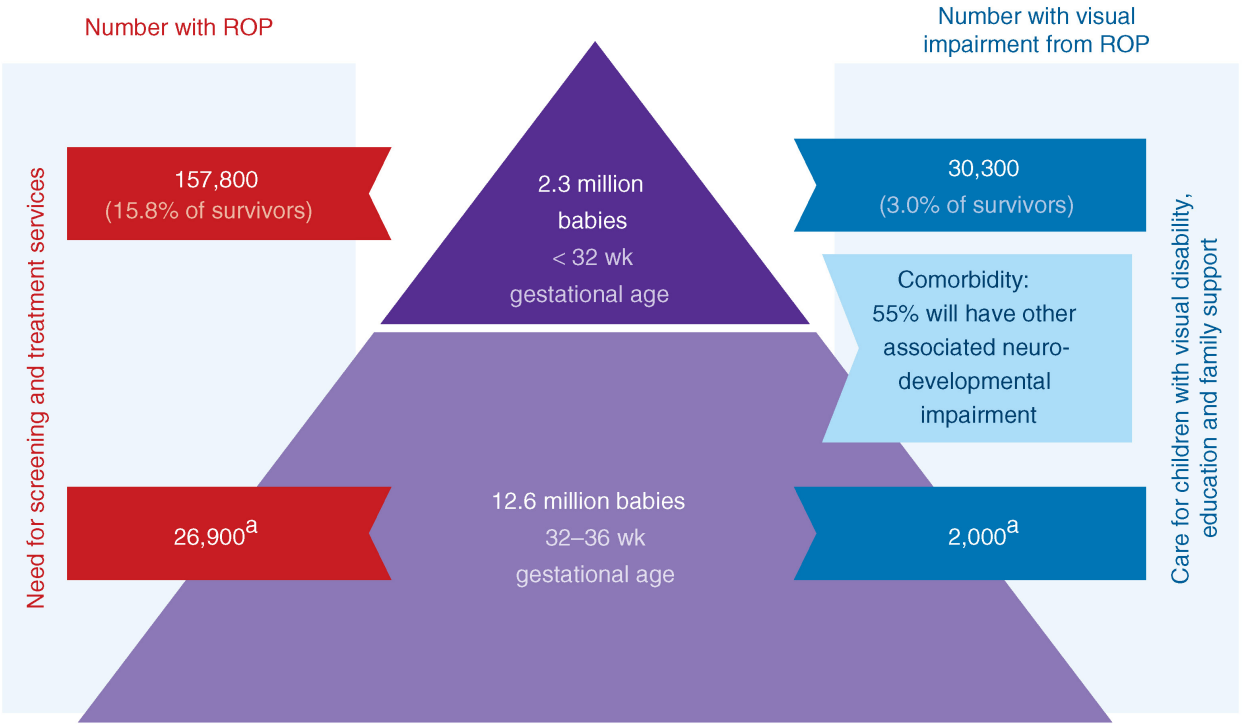
Cheap and robust devices to accurately capture and record time spent in the KMC position are greatly needed, as current methods typically involve increased workload (nurse report) or direct costs (observation), and may introduce bias (caregiver/nurse report, observation). Development of such a device would help facilitate research to determine the minimum dose of KMC required to achieve clinical benefits. For example, an existing neonatal wireless vital sign monitoring device could potentially be adapted to additionally track movement (e.g., between an incubator and the KMC position) by incorporating an accelerometer.[244] I am currently working with a team at the University of Cambridge who recently developed such a device to explore this possibility.

9.3.2.3. Cost-effective approaches for retinopathy screening and treatment in LMIC settings

An estimated 184,700 babies were affected by retinopathy of prematurity (ROP) in 2010, among which 32,300 developed visual impairment or blindness as a result (Figure 9-3).[195] In high-income countries, development of severe disease requiring treatment typically occurs only in

extremely preterm and ELBW babies.[245,246] In LMICs, severe ROP may develop in larger and more mature infants, e.g., those with birthweights of 1500-2000g or gestational ages of 32-36 weeks.[247,248] ROP requiring treatment is characterised by the presence of 'plus disease,' which is defined as arterial tortuosity and venous dilation of the posterior retinal vessels.[249] Sub-Saharan Africa is currently on the brink of an epidemic of ROP due to improved preterm survival coupled with neonatal care of inadequate quality, often inclusive of unmonitored and unblended oxygen therapy.[250–255] Expanded coverage of ROP screening and treatment services, together with improved quality of care, including pulse oximetry monitoring to maintain safe oxygen levels, will be essential to control the incidence of associated visual loss.[195,256]

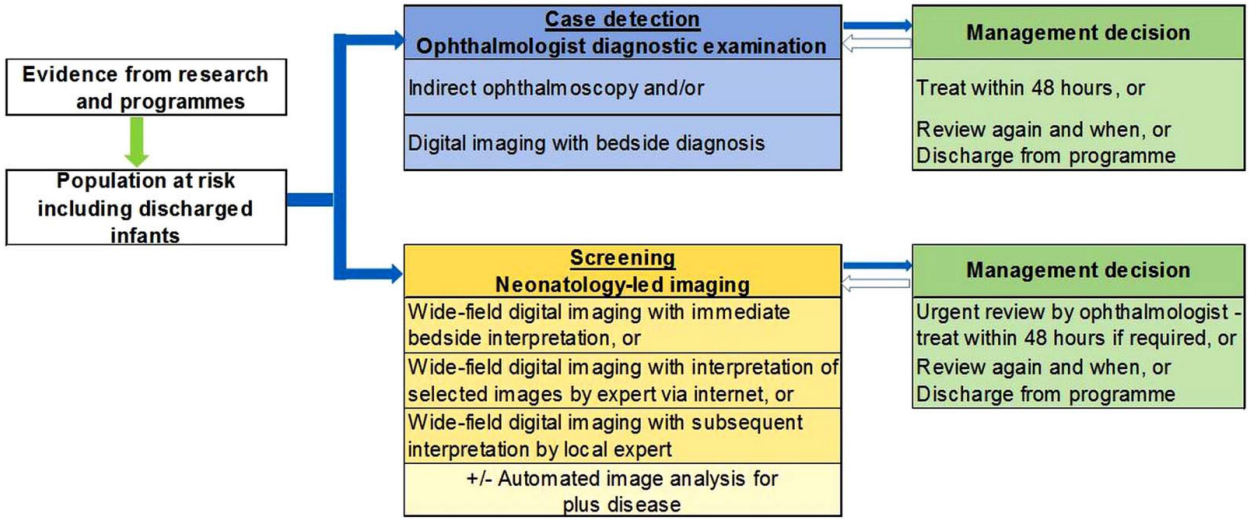
Figure 9-3. Retinopathy of prematurity and associated visual impairment among survivors of 15 million preterm births in 2010



Source: Blencowe et al, 2013.[195] [a] <1% of survivors following preterm birth at 32-36 weeks gestational age.

Most ROP screening and treatment programmes are led by ophthalmologists, who conduct frequent visits to neonatal units to examine at-risk infants, with clinical decisions at each visit (Figure 9-4).[257] Challenges of such programmes include shortages of ophthalmologists, travel burden, medicolegal concerns, poor reimbursement, and scheduling complexity.[257,258] Studies in the US, Canada, and India have demonstrated the validity of telemedicine platforms employing trained technicians or neonatal nurses to capture wide-angle digital retinal images, which can be interpreted at the bedside or remotely (Figure 9-4).[248,259–261]

Figure 9-4. Comparison of ophthalmology-led and neonatology-led approaches to detecting and monitoring progression of retinopathy of prematurity



Source: Gilbert et al, 2016.[257]

One US study found that a tiered approach utilising a telemedicine platform and a postnatal growth model for predicting severe ROP risk reduced the number of imaging sessions and ophthalmologist examinations more than either approach alone.[261] Notably, all studies included in the American Academy of Paediatrics Joint Technical Report on Telemedicine for the Evaluation of ROP utilised the RetCam™ imaging system (Clarity Medical Systems, Pleasanton, California, US),[262] which costs around US$100,000.[263] More recently, studies have demonstrated that fully automated image analysis algorithms using convolutional neural networks can accurately diagnose plus disease and quantitatively characterise pathological features of ROP.[264,265] Despite the considerable progress that has been made, there remains a pressing need for low-cost, high-resolution imaging technology that is suitable for ROP screening, as well for cost-effective approaches to expand coverage of ROP treatment services, especially in LMIC settings where ophthalmologists are few and the burden of resultant visual loss is high.[193,266] Importantly, such approaches should incorporate contextually-appropriate screening criteria that are wide enough to capture the majority of infants developing severe disease.[247,250]

9.3.3. Delivery

9.3.3.1. Validate and integrate indicators to track KMC coverage and quality

To improve care and facilitate research, indicators to track KMC coverage and quality through routine health information systems should be validated and integrated across levels of the health system. Such indicators should integrate clear definitions for the individual components of KMC,

including SSC, breastfeeding, early discharge, and follow-up. Progress in operationalising KMC has been hindered by the fact that previous studies have employed heterogeneous definitions, as well as by the scarcity of existing evidence on the effects of these individual components alone or in combination.[62] Future research and implementation programmes should prioritise collecting data on all aspects of KMC practice, including initiation criteria; target and actual duration of SSC per day (or per session, if intermittent KMC); caregiver involvement; IV fluids and feeding support, including breastmilk volume and mode of delivery; hospital discharge criteria; and follow-up guidelines.

9.3.3.2. Further validate the NMR-2000 score in LMICs and evaluate its utility to support clinical decision-making and inform resource allocation

Future research is required to further validate the NMR-2000 score in low-resource settings, using adequately powered samples. Studies employing large, multi-hospital datasets from Kenya and Uganda are being planned to address this gap. As discussed in the previous chapter, facilities in LMICs frequently experience human resource constraints, especially shortages of trained neonatal nurses.[33,34] In the aforementioned bottleneck analysis, 10 of 12 countries identified scarcities of skilled newborn care providers as a significant issue; recommendations included comprehensive mapping of the neonatal workforce and shifting of physician tasks that could be performed by lower level health workers (e.g., prescribing antibiotics) to maximise available resources.[34] Future research should explore the usefulness of the NMR-2000 score for supporting clinical decision-making and informing resource allocation,[133,198] including nursing workload. If found to be effective, this tool could be employed alongside other contextually-appropriate approaches, such as task shifting, to help address provider shortages in LMIC neonatal units.

9.3.3.3. Compare the clinical cascade model with other facility readiness assessment tools

Future research is also needed to compare the clinical cascade model with other facility readiness assessment tools, such as facility inventories and signal functions, across levels of neonatal care. Some tracer items for neonatal care are poorly defined (e.g., type of IV fluid, size of ventilation bag and mask),[34,125] and few previous studies evaluating EmONC readiness have employed clinical guidelines as tracer items.[221,267,268] To standardise readiness indicators and facilitate comparability across studies and settings, use of clearly defined tracers and inclusion of core clinical guidelines are essential. In addition, future research should explore the association between aggregate readiness loss and neonatal mortality in a variety of LMIC contexts.

9.3.3.4. Rigorous economic evaluations of KMC, including KMC before stabilisation, relative to standard care from the societal perspective, considering impact on women and households

Published economic and costing evaluations have consistently found that KMC resulted in cost savings for the hospital or provider relative to standard care. Such studies have included a multi-centre RCT in Mexico, Ethiopia, and Indonesia,[71] a RCT at one hospital in Colombia,[269] and implementation studies in one Nicaraguan[270] and one Brazilian hospital,[271] all of which compared KMC and incubator care among LBW neonates. An evaluation at 18 neonatal units in the UK estimated that providing KMC to 800 additional babies, initiated according to pre-defined clinical criteria,[272] could generate potential cost savings of £668,000 to £2 million annually, primarily as a result of reduced LOS.[273] More recently, an analysis of maternal and neonatal heath interventions in Ethiopia reported that achieving a 20% increase in KMC coverage relative to baseline would be highly cost-effective, with an incremental cost-effectiveness ratio of US$8 per disability-adjusted life year averted.[274] Notably, none of these studies has considered whether KMC may increase costs to households nor specifically evaluated the cost implications of initiating KMC prior to stabilisation. The OMWaNA economic evaluation will compare the incremental costs and cost-effectiveness of KMC and standard care from the societal perspective (provider and household combined),[275] considering variation in household costs and health outcomes across socioeconomic groups, as well as cost variation between hospitals and how these may differ outside the trial setting. Rigorous economic analyses of KMC, including the costs of initiating KMC before stabilisation, are warranted to examine incremental cost and cost-effectiveness relative to standard care from the societal perspective, particularly considering impact on women and households, in additional LMIC contexts.

9.4. Conclusion

Improved quality and coverage of inpatient care for small and sick newborns is urgently needed to reduce the estimated annual burden of 2.5 million neonatal deaths, the majority of which occur before stabilisation in settings without intensive care. Sub-Saharan Africa and south Asia account for around two-thirds of the 21 million LBW and 15 million preterm babies born every year, and together these regions are responsible for nearly 80% of newborn deaths. KMC is an evidence-based intervention that reduces mortality and morbidity among stable neonates weighing 2000g or less; however, its impact among newborns prior to stabilisation remains uncertain. This PhD has developed a clinical cascade model to assess facility readiness for neonatal care, validated a score to assess individual mortality risk and guide resource provision, and demonstrated the feasibility and acceptability of initiating KMC before stabilisation in sub-Saharan African contexts. These studies have informed the design and implementation of the OMWaNA trial, which aims to determine the mortality impact of KMC initiated before stabilisation relative to standard care at four hospitals in Uganda. The findings of this RCT are expected to have broad applicability to hospitals in LMICs and could inform policies and programmes to promote survival and prevent disability among small and sick newborns, particularly in settings where intensive care is not available. The economic evaluation will compare the incremental costs and cost-effectiveness of KMC and standard care, taking into consideration opportunity costs for families, which will be important to promote KMC continuity. The process evaluation will strengthen understanding of KMC initiation before stabilisation through exploration of barriers, facilitators, and pathways underlying clinical effects, with implications for the transferability of results and, if shown to be effective, future scale-up efforts. Follow-up work is needed to advance scientific understanding of neurodevelopmental outcomes after KMC as well as the effects of KMC on mental health and wellbeing among both mothers and babies. Investment in improving coverage of comprehensive intervention packages for inpatient newborn care is required to address the growing global burden of death and disability following neonatal conditions. Wider implementation of KMC coupled with high quality, family-integrated neonatal care could alleviate nursing workload, empower mothers and caregivers, and enable the most vulnerable newborns to survive and thrive.

Images: UCSF Preterm Birth Initiative, with caregiver consent for publication

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11. Annexes

A.1. Contributions by the candidate and others to work presented in this thesis

Table A1-1. Contributions by the candidate and others to work presented in this thesis

Chapter	Component (or paper if relevant)	Activity	Responsibility	Additional input
Chapter 1	Background	Conceptualisation and writing	**Melissa Medvedev**	Review by Joy Lawn, Elizabeth Allen, Diana Elbourne, Cally Tann
Chapter 2	Aim and objectives	Conceptualisation and writing	**Melissa Medvedev**	Review by Joy Lawn, Elizabeth Allen, Diana Elbourne, Cally Tann
Chapter 3	Clinical cascades to assess physical readiness of facilities for the care of small and sick neonates in Kenya and Uganda (Paper A)	Conceptualisation of paper	**Melissa Medvedev**, John Cranmer, Dilys Walker	
		Development of facility readiness cascades	**Melissa Medvedev**, Harriet Nambuya, Grace Nalwa, Gertrude Namazzi	Peter Waiswa, Phelgona Otieno, Dilys Walker
		Collection of facility assessment data in Kenya and Uganda	Phillip Wanduru, Kevin Achola, Christopher Omondi Otare, Pricah Lihanda	**Melissa Medvedev**, Harriet Nambuya, Grace Nalwa, Gertrude Namazzi, Peter Waiswa, Phelgona Otieno
		Analysis of data	**Melissa Medvedev**	Hilary Spindler, John Cranmer
		Drafting of manuscript	**Melissa Medvedev**	
		Design of cascade figures	Damien Scogin	**Melissa Medvedev**
		Review of drafts and approval of final version	All authors	
Chapter 4	Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 grams or less: an analysis using retrospective data from the UK National Neonatal Research Database and The Gambia (Paper B)	Conceptualisation of paper	**Melissa Medvedev**, Cally Tann, Diana Elbourne, Joy Lawn, Elizabeth Allen	
		Study design	**Melissa Medvedev**, Helen Brotherton, Cally Tann, Diana Elbourne, Joy Lawn, Elizabeth Allen	
		Literature review of neonatal risk scores	**Melissa Medvedev**	Review by Joy Lawn
		Curation of data from UK National Neonatal Research Database	**Melissa Medvedev**, Christopher Gale, Cally Tann	
		Collection of validation data in The Gambia	Helen Brotherton, Abdou Gai	**Melissa Medvedev**
		Model development and validation analyses	**Melissa Medvedev**	Review by Elizabeth Allen

Chapter	Component (or paper if relevant)	Activity	Responsibility	Additional input
		Drafting of manuscript	**Melissa Medvedev**	
		Review of drafts and approval of final version	All authors	
Chapter 5	Current evidence regarding duration, timing, clinical impact, and causal pathways for clinical effects of kangaroo mother care: literature review	Conceptualisation and writing	**Melissa Medvedev**	Review by Joy Lawn, Elizabeth Allen, Diana Elbourne, Cally Tann
		Review of literature evaluating KMC duration, timing, effect on mortality and other clinical outcomes, causal pathways for clinical effects of KMC	**Melissa Medvedev**	Review by Joy Lawn, Cally Tann
Chapter 6	Kangaroo Mother Care for clinically unstable neonates: is it feasible at a hospital in Uganda? (Paper C)	Conceptualisation of paper	**Melissa Medvedev**, Joy Lawn	
		Study design	**Melissa Medvedev**, Joy Lawn	Peter Waiswa, Cally Tann, Diana Elbourne, Janet Seeley, Elizabeth Allen
		Design of data collection tools and interview guides	**Melissa Medvedev**	Harriet Nambuya, Diana Elbourne, Janet Seeley
		Collection of audit data	Justine Inhensiko, Victoria Kyobutungi	**Melissa Medvedev**, Harriet Nambuya, Peter Waiswa
		Collection of clinical data	Samuel Atepo, Victoria Kyobutungi	**Melissa Medvedev**, Harriet Nambuya, Peter Waiswa
		Coordination and conduct of interviews	Vanessa Akinyange, Victoria Kyobutungi	**Melissa Medvedev**, Harriet Nambuya, Peter Waiswa
		Analysis of data	**Melissa Medvedev**	
		Drafting of manuscript	**Melissa Medvedev**	
		Review of drafts and approval of final version	All authors	
Chapter 7	Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa (OMWaNA): protocol for a randomised controlled trial to examine mortality impact in Uganda (Paper D)	Conceptualisation of trial	**Melissa Medvedev**, Joy Lawn	
		Study design and preparation of *Joint Global Health Trials* funding application	**Melissa Medvedev**, Joy Lawn	Cally Tann, Elizabeth Allen, Peter Waiswa, Diana Elbourne, Catherine Pitt
		Drafting of trial protocol	**Melissa Medvedev**	Joy Lawn, Cally Tann, Peter Waiswa, Ruth Canter, Helen Brotherton, Diana Elbourne, Elizabeth Allen
		Design of economic evaluation	Elizabeth Ekirapa-Kiracho, Kenneth Katumba, Catherine Pitt	**Melissa Medvedev**, Joy Lawn
		Design of women's wellbeing evaluation	Giulia Greco	Elizabeth Ekirapa-Kiracho, Kenneth

Chapter	Component (or paper if relevant)	Activity	Responsibility	Additional input
				Katumba, Catherine Pitt
		Design of process and qualitative evaluations	**Melissa Medvedev**, Cally Tann, Joy Lawn	Victor Tumukunde, Peter Waiswa, Janet Seeley, Diana Elbourne
		Preparation of case report forms and standard operating procedures	Victor Tumukunde, Ivan Mambule, Ruth Canter, Kenneth Katumba, **Melissa Medvedev**, Cally Tann	Peter Waiswa, Christian Hanson, Elizabeth Ekirapa-Kiracho, Helen Brotherton, Diana Elbourne, Elizabeth Allen, Joy Lawn
		Protocol implementation	Victor Tumukunde, Ivan Mambule, **Melissa Medvedev**, Cally Tann, Ruth Canter, Kenneth Katumba	Joy Lawn, Peter Waiswa, Elizabeth Allen, Moffat Nyirenda, Diana Elbourne, Elizabeth Ekirapa-Kiracho, Catherine Pitt
		Drafting of manuscript	**Melissa Medvedev**	
		Review of drafts and approval of final version	All authors	
Chapter 8	Discussion and implications	Conceptualisation and writing	**Melissa Medvedev**	Review by Joy Lawn, Elizabeth Allen, Peter Waiswa, Diana Elbourne, Cally Tann
Chapter 9	Recommendations and conclusion	Conceptualisation and writing	**Melissa Medvedev**	Review by Joy Lawn, Elizabeth Allen, Peter Waiswa, Diana Elbourne, Cally Tann

A.2. Observation study showed that the continuity of skin-to-skin contact with low birth weight infants in Uganda was suboptimal

A.2.1. Scope of this paper

Heather Watkins (Cooper) was a MSc student at LSHTM in 2015-2016 whom I co-supervised with Professor Lawn. Ms. Watkins conducted a mixed methods study to explore current KMC practices in Uganda, using facility-based observations of SSC and interviews with mothers practicing home-based KMC after discharge. This paper presents the findings of the observational study, which aimed to quantify the daily duration of SSC over the first week of life amongst stabilised newborns ≤2000g at Jinja Hospital, and discusses reasons for suboptimal continuity.

A.2.2. Citation

Watkins HC, Morgan MC, Nambuya H, Waiswa P, Lawn JE. Observation study showed that the continuity of skin-to-skin contact with low birth weight infants in Uganda was suboptimal. *Acta Paediatr* 2018; 107: 1541-1547. doi: 10.1111/apa.14344.

A.2.3. Copyright and permissions

A.2.4. Ethical approvals

Ethical approval was obtained from LSHTM, Makerere University, and UNCST. Letters of approval from LSHTM, Makerere University, and UNCST are available on the following pages.

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MSc Research Ethics Committee

Ms. Heather Cooper
MSc Student
MSc Public Health (Public Health Stream)
LSHTM

31 May 2016

Dear Heather ,

Study Title: Kangaroo mother care practices in Jinja, Uganda: Facility-based observations and perceptions of home-based care

LSHTM MSc Ethics Ref: 10554

Thank you for responding to the MSc Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered by the Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application (CARE) form and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is contingent on local ethical approval having been received, where relevant. It is the responsibility of the student and their supervisor to ensure appropriate local ethical approval is in place before a study commences (ie if you indicated this in question 40, local approval is required).

Please forward confirmation of local ethics approval as soon as it is received.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	CV Heather Cooper	19/02/2016	1
Information Sheet	Consent_Observations_English	21/02/2016	1
Information Sheet	Consent_Observations_Lusoga	21/02/2016	1
Information Sheet	Consent_Interview_English	21/02/2016	1
Information Sheet	Consent_Interview_Lusoga	21/02/2016	1
Protocol / Proposal	KMC_Parent_Recording_Sheet_English	22/02/2016	1
Protocol / Proposal	KMC_Parent_Recording_Sheet_Lusoga	22/02/2016	1
Protocol / Proposal	Interview_Guide_English	22/02/2016	1
Protocol / Proposal	Interview_Guide_Lusoga	22/02/2016	1
Protocol / Proposal	Observational_Data_Collection_Form_Version2	26/03/2016	1
Protocol / Proposal	LEO Study Proposal	26/03/2016	1
Information Sheet	Consent_Interview_English_Version 2	19/05/2016	2
Information Sheet	Consent_Interview_Lusoga_Version 2	19/05/2016	2
Information Sheet	Consent_Observations_English_Version 2	19/05/2016	2
Information Sheet	Consent_Observations_Lusoga_Version 2	19/05/2016	2
Protocol / Proposal	KMC_Parent_Recording_Sheet_English	19/05/2016	2
Protocol / Proposal	KMC_Parent_Recording_Sheet_Lusoga	19/05/2016	2
Protocol / Proposal	Interview_Guide_English_Version 2	19/05/2016	2
Protocol / Proposal	Interview_Guide_Lusoga_Version 2	19/05/2016	2
Protocol / Proposal	Observations_Data Collection_Version 2_Lusoga	24/05/2016	2

Protocol / Proposal	Version 2 KMC_Study_Proposal	24/05/2016	2
Covering Letter	Cover Letter - Responses to LSHTM Ethics	24/05/2016	1

After ethical review

Any subsequent changes to the application must be submitted to the Committee via an Amendment form on the ethics online applications website. Ethics online applications website link: http://leo.lshtm.ac.uk

Yours sincerely,

Dr Cicely Marston
Chair

mscethics@lshtm.ac.uk
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COLLEGE OF HEALTH SCIENCES
SCHOOL OF PUBLIC HEALTH
HIGHER DEGREES, RESEARCH AND ETHICS COMMITTEE

May 27th, 2016

Heather Cooper
Principal Investigator, Protocol (400) - MSc Candidate, Public Health
Faculty of Epidemiology & Population Health
London School of Hygiene & Tropical Medicine

Re: Approval of Proposal titled: Kangaroo mother care practices in Jinja, Uganda: Facility-based observations and perceptions of home-based care

This is to inform you that, the Higher Degrees, Research and Ethics Committee (HDREC) has granted approval to the above referenced study, the HDREC reviewed the proposal during the 138th meeting 12th/04/2016 and provided some suggestions and comments which you have adequately incorporated:

Please note that your study protocol number with HDREC is **400**. Please be sure to reference this number in any correspondence with HDREC. Note that the initial approval date for your proposal by HDREC is 27th/05/2016, and therefore approval expires at every annual anniversary of this approval date. The current approval is therefore valid until: **26th/05/2017**.

Continued approval is conditional upon your compliance with the following requirements:

1) No other consent form(s), questionnaire and/or advertisement documents should be used. The consent form(s) must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject must be given a copy of the signed consent form.

2) All protocol amendments and changes to other approved documents must be submitted to HDREC and not be implemented until approved by HDREC except where necessary to eliminate apparent immediate hazards to the study subjects.
3) Significant changes to the study site and significant deviations from the research protocol and all unanticipated problems that may involve risks or affect the safety or welfare of subjects or others, or that may affect the integrity of the research must be promptly reported to HDREC.
4) All deaths, life threatening problems or serious or unexpected adverse events, *whether related to the study or not,* must be reported to HDREC in a timely manner as specified in the National Guidelines for Research Involving Humans as Research Participants.

- Please complete and submit reports to HDREC as follows:

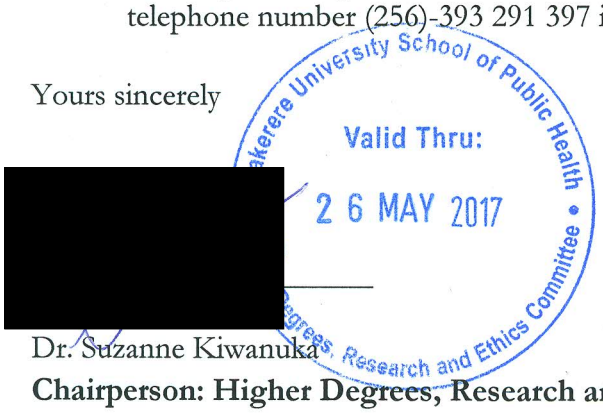
Makerere University School of Public Health
Valid Thru:
26 MAY 2017
Higher Degrees, Research and Ethics Committee

a) For renewal of the study approval – complete and return the continuing Review Report – Renewal Request (Form 404A) at least 60 days prior to the expiration of the approval period. The study cannot continue until re-approved by HDREC.

b) Completion, termination, or if not renewing the project – send a final report within 90 days upon completion of the study.

- Finally, the legal requirement in Uganda is that all research activities must be registered with the National Council of Science and Technology. The forms for this registration can be obtained from their website www.uncst.go.ug. Please contact the Administrative Assistant of the Higher Degrees, Research and Ethics Committee at wtusiime@musph.ac.ug or telephone number (256)-393 291 397 if you encounter any problems.

Yours sincerely



Dr. Suzanne Kiwanuka
Chairperson: Higher Degrees, Research and Ethics Committee

Enclosures:

a) A stamped, approved study documents (informed consent documents):

Uganda National Council for Science and Technology

(Established by Act of Parliament of the Republic of Uganda)

Our Ref: HS 2078

11th July 2016

Heather Ryan Cooper
C/o School of Public Health
Makerere University
Kampala

Re: Research Approval: Kangaroo Mother Care Practices in Jinja, Uganda: Facility-Based Observations and Perceptions of Home-Based Care

I am pleased to inform you that on **27/06/2016**, the Uganda National Council for Science and Technology (UNCST) approved the above referenced research project. The Approval of the research project is for the period **27/06/2016** to **27/06/2017.**

Your research registration number with the UNCST is **HS 2078**. Please, cite this number in all your future correspondences with UNCST in respect of the above research project.

As Principal Investigator of the research project, you are responsible for fulfilling the following requirements of approval:

1. All co-investigators must be kept informed of the status of the research.
2. Changes, amendments, and addenda to the research protocol or the consent form (where applicable) must be submitted to the designated Research Ethics Committee (REC) or Lead Agency for re-review and approval prior to the activation of the changes. UNCST must be notified of the approved changes within five working days.
3. For clinical trials, all serious adverse events must be reported promptly to the designated local REC for review with copies to the National Drug Authority.
4. Unexpected events involving risks to research subjects/participants must be reported promptly to the UNCST. New information that becomes available which alters the risk/benefit ratio must be submitted promptly for UNCST review.
5. Only approved study procedures are to be implemented. The UNCST may conduct impromptu audits of all study records.
6. A progress report must be submitted electronically to UNCST within four weeks after every 12 months. Failure to do so may result in termination of the research project.

Below is a list of documents approved with this application:

	Document Title	Language	Version	Version Date
1.	Research proposal	English	N/A	N/A
2.	Data Collection Form	English and Lusoga	N/A	N/A
3.	Kangaroo Mother Care Bedside Recording Sheet	English and Lusoga	N/A	N/A
4.	Interview Topic Guide	English and Lusoga	N/A	N/A
5.	Participant Information Sheet and Consent Form	English and Lusoga	N/A	N/A

Yours sincerely,

Hellen. N. Opolot
for: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

cc. Chair, Makerere University School of Public Health Higher Degrees, Research Ethics Committee

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student ID Number	131393	**Title**	Dr
First Name(s)	Melissa Morgan		
Surname/Family Name	Medvedev		
Thesis Title	Informing the design of a trial of kangaroo mother care initiated before stabilisation amongst small and sick newborns in a sub-Saharan African context using mixed methods		
Primary Supervisor	Elizabeth Allen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Acta Paediatrica as: Watkins HC, Morgan MC, Nambuya H, Waiswa P, Lawn JE. Observation study showed that the continuity of skin-to-skin contact with low birth weight infants in Uganda was suboptimal. Acta Paediatr. 2018; 107: 1541-1547. doi: 10.1111/apa.14344.		
When was the work published?	March 2018		
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Ms. Heather Watkins (Cooper) was a MSc student at LSHTM in 2015-2016 whom I co-supervised with Prof. Joy Lawn. I provided substantial input to Ms. Watkins throughout study design, protocol writing, creation of data collection tools, and acquistion of ethics approvals, with oversight by Prof. Lawn. Ms. Watkins collected data in Uganda under the supervision of Drs. Peter Waiswa and Harriet Nambuya. Ms. Watkins conducted all analyses, with input from myself and Prof. Lawn. I contributed to the review of KMC trials amongst stabilised infants in the manuscript introduction. Ms. Watkins wrote the first draft of the manuscript, with substantial input from myself and Prof. Lawn. Ms. Watkins prepared all subsequent revisions, with consideration of comments from all co-authors.

SECTION E

Student Signature	Melissa Medvedev
Date	27th January 2020

Supervisor Signature	Elizabeth Allen
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REGULAR ARTICLE

Observation study showed that the continuity of skin-to-skin contact with low-birthweight infants in Uganda was suboptimal

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Kangaroo mother care, Low birthweight, Neonatal mortality, Preterm infant, Skin-to-skin contact

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ABSTRACT

Aim: Kangaroo mother care (KMC) is a safe and effective method of reducing neonatal mortality in resource-limited settings, but there has been a lack of data on the duration of skin-to-skin contact (SSC) in busy, low-resource newborn units. Previous studies of intermittent KMC suggest the duration of SSC ranged from 10 minutes to 17 hours per day.

Methods: This was an observational study of newborn infants born weighing less than 2000 g, which collected quantitative data on SSC over the first week after birth. The study took place in July 2016 in the newborn unit of a low-resource facility in Uganda.

Results: The mean daily duration of SSC over the first week after birth was three hours. This differed significantly from the World Health Organization recommendation of at least 20 hours of SSC per day. SSC was provided by mothers most of the time (73.5%), but other family members also took part, especially on the day of birth.

Conclusion: Our study found a disappointingly low daily duration of SSC in this Ugandan newborn unit. However, advocacy and community education of SSC may help to decrease the stigma of KMC, improve overall acceptance and reduce the age at SSC initiation.

INTRODUCTION

Nearly half of all deaths in children under five occur during the neonatal period. Complications of preterm birth, defined as birth before 37 completed weeks of gestation, were responsible for 35% of the 2.7 million neonatal deaths across the globe in 2015 (1). Low-birthweight, defined by the World Health Organization (WHO) as weighing less than 2500 g at birth, irrespective of gestational age, has been used as a surrogate for preterm birth (2,3) and is correlated with neonatal survival (2,4,5). Estimates suggest that at least 75% of global neonatal deaths occur in low-income and middle-income countries (6), where neonatal intensive care is often not available (7).

Kangaroo mother care (KMC) is an alternative to conventional thermal care for infants considered to be clinically stable (7). Key features of KMC are early, continuous and prolonged skin-to-skin contact (SSC) between the infant and the mother or another caregiver, frequent and exclusive breastfeeding, early discharge from hospital, whenever possible, and postdischarge follow-up (2,3). KMC provides the infant with thermal support, protection from infection, appropriate stimulation and a nurturing environment (3,8,9).

Evidence supports KMC as a safe and effective way of reducing neonatal mortality (2,7,9,10). In 2015, the WHO issued a strong recommendation that KMC should be part of the routine care of newborn infants weighing up to 2000 g at birth and that it should be initiated in healthcare facilities as soon as infants were clinically stable (11). The WHO recommendations advocate continuous KMC, defined as at least 20 hours of SSC per day. Where

Abbreviations
KMC, Kangaroo mother care; SSC, Skin-to-skin contact; WHO, World Health Organization.

Key notes

- Data on Kangaroo mother care (KMC) and the duration of skin-to-skin contact (SSC) in busy, low-resource newborn units are lacking.
- This study found that the mean daily duration of SSC provided to low-birthweight infants admitted to a newborn unit in Uganda was three hours.
- SSC was mostly provided by mothers (73.5%), but other family members also took part, especially on the day of birth.

continuous KMC is not feasible, intermittent SSC is preferable to conventional thermal care (11).

Prolonged direct SSC between infants and caregivers is the cornerstone of KMC (12). Most studies of KMC have taken place in dedicated KMC wards (13–18), where staff were trained to care for both newborn infants and postpartum women. Intermittent SSC may occur in the absence of a KMC ward or where adequate space to practice continuous SSC does not exist or is not used.

The 2016 Cochrane Review of KMC included 21 randomised controlled trials (RCT), three of which evaluated continuous KMC in stabilised infants (Table 1) (7). These three studies took place in neonatal intensive care units (NICU) or KMC wards at maternity, university or tertiary care hospitals. The review also evaluated 16 RCTs of intermittent KMC in stabilised infants and found that the mean daily duration of SSC in these trials ranged from 10 minutes to 17 hours per day (Table 2). Most of these studies also took place in NICUs, intermediate nurseries or maternity wards in tertiary care hospitals. When infants were not receiving SSC, they were kept in incubators or under radiant warmers. The remaining two RCTs included in the Cochrane Review evaluated KMC in infants prior to stabilisation.

None of the RCTs of intermittent KMC took place in sub-Saharan Africa, and none of the studies evaluated KMC in an environment without a KMC ward or other dedicated space for KMC. Quantitative descriptions of the duration of SSC have rarely been reported (3). Many studies have only stated whether KMC is practised in a facility (19) or how health workers promote KMC, such as advising mothers to provide SSC to their infants at all times, except for brief interruptions to use the bathroom (15). Other studies have described KMC as irregular (20) or almost continuous (21). On the rare occasions when the hours of SSC are recorded, details on whether the data were obtained through observation, self-report or other methods were not provided (13).

Lack of data on the duration of SSC in routine practice has been cited as a limitation in the current evidence (3), and poor-quality data on low-birthweight infants are a significant barrier to KMC success (12). This study aimed to address the knowledge gap surrounding the continuity of facility-based KMC through direct observation of SSC in a busy newborn unit at a resource-limited hospital in Uganda. The objectives were to quantify the daily duration of SSC over the first week of life and to compare these findings with the data collected on SSC continuity by the existing literature.

METHODS

This was an observational study of newborn infants that collected quantitative data on SSC practices in July 2016. A sample of participants was recruited after birth using the following inclusion criteria: inborn, born weighing up to 2000 g, deemed clinically stable by the admitting clinician and the mother was willing and able to participate in KMC. Infants were excluded from study if they were outborn, born outside the study period, born weighing greater than 2000 g, born with congenital anomalies or severe medical problems that precluded the safe use of KMC or the mother was unwilling or unable to participate in KMC. Ethical approval for this study was obtained from the London School of Hygiene and Tropical Medicine, Makerere University and the Uganda National Council of Science and Technology.

Study site

The study took place at Jinja Regional Referral Hospital in south-eastern Uganda. The hospital serves a catchment area of four million people and has approximately 6600 deliveries per year (22). Sick newborn infants are cared for in a newborn special care unit, adjacent to the labour ward. Common admitting diagnoses include prematurity, birth asphyxia, sepsis, respiratory distress syndrome and jaundice. During the study, the approximate daily occupancy was 10–15 patients and the unit had 13 cots, three radiant warmers and one incubator. A total of eight midwives and nurses staffed the newborn unit on a rotating day–night schedule, with one or two working per shift.

Data collection

A data collection tool, based upon the WHO's KMC guide (2) was specifically designed for this study. When eligible newborn infants were admitted to the newborn unit, we immediately obtained informed consent from the mother or father. When no family members accompanied the patient on admission, we visited the mother in the labour ward to

Table 1 Randomised controlled trials of the Cochrane Review* evaluating continuous KMC (20 hours) in stabilised newborn infants

Study	Setting (country; type of facility)	Mean age at recruitment	Source of temperature control for conventional care (control) group
Cattaneo et al. (1998) (23) (n = 285)	Ethiopia, Mexico and Indonesia; neonatal units of university hospitals	Median age 10 days (1–74) in KMC group (n = 149); 8 days (1–40) in control group (n = 136)	Radiant warmer or open crib in warm room in Ethiopia; Incubators in Mexico and Indonesia
Charpak et al. (1997) (24) (n = 777)	Colombia; Kangaroo Mother Care ward or neonatal intensive care unit of tertiary care hospital	Median age 4 days (1–60) in KMC group (n = 396); 3 days (1–55) in control group (n = 381)	Incubator until able to regulate temperature and thriving
Sloan et al. (1994) (25) (n = 300)	Ecuador; neonatal intensive care unit of maternity hospital	13.0 days ± 10.5 in KMC (n = 140) and control (n = 160) groups	Incubator or radiant warmer

*Conde-Agudelo and Díaz-Rossello JL (7).

Table 2 Randomised controlled trials of the Cochrane Review* evaluating intermittent KMC in stabilised newborn infants

Study	Setting (country, type of facility)	Mean age at recruitment	Source of thermal care for control group	Mean daily hours of KMC
Nimbalkar et al. (2014) (26) (n = 45)	India; maternity ward	43 minutes ± 13 in KMC group (n = 22); 30–60 minutes in control group (n = 23)	Radiant warmer	17.0 ± 0.3 during first 24 hours; KMC discontinued at 24 hours
Suman et al. (2008) (27) (n = 220)	India; neonatal intensive care unit of tertiary care hospital	3.7 days ± 2.8 in KMC group (n = 108); 2.3 days ± 1.9 in control group (n = 112)	Radiant warmer	13.5
Kumbhojkar et al. (2016) (28) (n = 120)	India; neonatal intensive care unit of university hospital	3 days in KMC group (n = 60); 4 days in control group (n = 60)	Radiant warmer	11.5
Gathwala et al. (2008) (29) (n = 110)	India; neonatal unit of university hospital	1.7 days ± 0.5 in KMC (n = 50) and control (n = 50) groups	Incubator or radiant warmer	10.2 ± 1.5 in the first month
Eka Pratiwi et al. (2009) (30) (n = 93)	Indonesia; neonatal intensive care unit of public hospital	Not provided (n = 48 KMC group; n = 45 control group)	Incubator or open crib in warm room	10.0 ± 1.8 (range 5.3–13.5)
Kadam et al. (2005) (31) (n = 89)	India, neonatal intensive care unit of tertiary care hospital	3.2 days (1–8) for KMC (n = 44) and control (n = 45) groups	Radiant warmer	9.8 ± 3.7
Ghavane et al. (2012) (32) (n = 140)	India; Kangaroo Mother Care ward (KMC group), neonatal intensive/ intermediate care unit (control group) of tertiary care hospital	14.1 days ± 10.3 in KMC group (n = 71); 13.7 days ± 10.2 in control group (n = 69)	Incubator or radiant warmer	≥8, placed in open cribs when not in KMC
Ali et al. (2009) (33) (n = 114)	India; neonatal intensive care unit of tertiary care hospital	4.7 days ± 2.9 in KMC group (n = 58); 4.8 ± 2.4 in control group (n = 56)	Radiant warmer or open cot in warm room	6.3 ± 1.52 (range 4–12)
Acharya (et al.) (2014) (34) (n = 126)	Nepal; newborn nursery of tertiary care hospital	Not provided (n = 63 KMC group; n = 63 control group)	Radiant warmer	≥6
Neu and Robinson (2010) (35) (n = 60)	United States; initially neonatal intensive care unit of hospitals, then at home	15.0 days ± 6.7 for KMC group (n = 31); 15.0 days ± 4.9 for control group (n = 29)	Incubator while in hospital	4.81 ± 2.12 (participant reported data)
Ramanathan et al. (2001) (36) (n = 28)	India; neonatal intensive care unit of tertiary care hospital	Median age at KMC initiation 11.8 days for KMC (n = 14) group	Incubator or radiant warmer	≥4
Roberts et al. (2000) (37) (n = 30)	Australia; neonatal intensive care units of university or tertiary care hospitals	31.5 days ± 2.7 for KMC (n = 16) and control (n = 14) groups	Incubator	1.6 ± 0.9, 5 days a week
Rojas et al. (2003) (38) (n = 60)	United States; neonatal intensive care unit of tertiary care hospital	19.6 days in KMC group (n = 33); 18.2 days in control group (n = 27)	Incubator	1.3 ± 0.7
Boo and Jamli (2007) (39) (n = 128)	Malaysia; neonatal intensive care unit of tertiary care hospital	Median age 24.5 days in KMC group (n = 65); 20.5 days in control group (n = 63)	Incubator until infant reached 1750 g	1.0 (median)
Whitelaw et al. (1988) (40) (n = 71)	United Kingdom; neonatal intensive care unit of a university or tertiary care hospital	16 days (1–66) for KMC (n = 35) and control (n = 36) groups	Incubator	0.6 (0–1.5)
Blaymore Bier et al. (1996) (41) (n = 50)	United States; special care nursery of a tertiary care hospital	29 days in KMC group (n = 25); 30 days in control group (n = 25)	Incubator	0.2

*Conde-Agudelo and Díaz-Rossello JL (7).

obtain consent. Thus, continuous observation of infants began as soon as possible after birth and continued until the end of day of life seven, discharge or death, whichever came first. The lead researcher was present in the newborn unit during daytime hours, and trained study personnel were responsible for the data collection at night. The unit was small, so it was possible to monitor multiple subjects simultaneously. The characteristics of the mothers and infants were documented using hospital records or by asking the mother when information was not documented.

For each day of life, the total duration of hours spent in SSC was calculated by adding together the duration of all individual SSC sessions on that day. If an infant received at least 20 hours of SSC, it was considered continuous KMC, and any fewer hours of SSC per day was documented as intermittent KMC (7). If the practice was intermittent, one of the following reasons was recorded: mother ill, infant unstable, caregiver not available or environmental challenges.

The date and time of birth and of the first SSC session in the newborn unit were recorded and, from this, the age in hours at SSC initiation was determined. We recorded the hours spent in SSC, the caregiver providing SSC, the infant position and infant clothing for every session of SSC.

A well-positioned infant was defined as an infant meeting four of the following five criteria: upright, between the mother's breasts, abdomen and chest touching the mother's bare chest, head turned to one side, legs flexed and abducted. Appropriate clothing meant the infant's chest and abdomen were exposed and the infant was wearing a hat.

Data analysis

All the data collected on written data collection forms were entered using EpiData 3.1 (EpiData Association, Odense, Denmark). Data were double-entered, checked for any incongruence and exported to Stata 14 (Stata Corp, College Station, TX, USA) for analysis. The primary outcome was the cumulative daily duration of SSC over the first week of life. This was compared to the WHO recommendations using a *t*-test. The secondary outcomes were age at SSC initiation, the duration of individual SSC sessions, the reason for intermittent KMC, the SSC provider, the infant's position and infant's clothing. Descriptive statistics for continuous variables included the means, standard deviations (SD) and ranges. Categorical variables were analysed and presented as frequencies and proportions. We considered conducting a survival analysis of KMC per day per baby still in hospital, but we decided against this given the small sample size.

RESULTS

Sample

Of the 68 newborn infants admitted to the unit during the study period, 12 met the inclusion criteria. None of the parents who were approached refused to participate. The average age of the mothers was 24 ± 5 years; the enrolled infants had a mean birthweight of 1664 ± 300 g and a mean completed gestational age of 31 ± 3 weeks determined by last menstrual period. Half of enrolled infants were male, and 67% were delivered vaginally.

Of the 12 participants, eight were observed for the entire first week of life, one died on day of life two and one left against medical advice on day of life four. In total, 117 individual SSC sessions were observed, and information on daily totals was gathered 76 times.

Outcomes

The mean daily duration of SSC over the first week of life was 3.0 ± 2.1 hours (range 0–9). When compared to the WHO recommendation for at least 20 hours of SSC per day, the resulting p value was <0.0001. This was evidence of a significant difference between the practice at this facility and the WHO recommendations.

We found that the mean daily duration of SSC, age at SSC initiation and total number of SSC sessions varied by participant and was not related to birthweight (Table 3). The mean age at SSC initiation in the newborn unit was 21.6 ± 9.8 hours (range 5.5–44.5). The mean duration of individual SSC episodes was 1.9 ± 0.5 hours (range 1.0–3.5).

None of the infants received continuous KMC. We explored reasons for the lack of KMC continuity. The mother was ill 23.7% of the time, and the infant was considered too unstable for KMC 1.3% of the time. Most of the time (75.0%), however, the reason for intermittent SSC was environmental challenges, such as overcrowding, lack of privacy or shortage of chairs for caregivers. Although a small KMC room exists just outside the newborn unit, it was not used frequently. Caregivers sat in plastic chairs or on the floor of the crowded unit while providing SSC and privacy screens were not available.

Skin-to-skin contact was mainly provided by mothers (73.5%), but other family members also took part, especially on the day of birth (Fig. 1). Newborn infants were well-positioned and wearing appropriate clothing during all SSC sessions.

DISCUSSION

The most SSC occurred on the second day of life and this was the only day where every infant received at least one session of SSC. Infants received the least SSC on the day of birth. Infants who received the greatest number of SSC sessions over the first week had higher mean daily durations of SSC compared to infants receiving fewer sessions. Unfortunately, the duration of SSC did not increase over the first week, as some literature has suggested (8,11). The shortest SSC sessions were one hour and the longest were 3.5 hours. While many studies on KMC conclude that SSC should be practiced for no less than one hour (7), two hours is ideal (8).

Most the time, both the mother and the infant were stable enough for KMC and a potential SSC provider was nearby and available. Once they were discharged from the labour ward, most mothers spent the day in the outdoor area adjacent to the newborn unit and other family members frequently visited.

Previous research suggests that many physical and cultural barriers to KMC exist. Physical barriers include issues such as lack of space, overcrowding, lack of privacy, absence of chairs or beds and the time needed to provide SSC (8,42–46). Existing customs, such as carrying the infant on the back, stigma surrounding the birth of a preterm infant and general poor involvement and support from the community may affect KMC. Beliefs that incubator care is more effective than SSC and ambivalence by medical staff may also influence the duration of SSC (12,43,45).

Mothers provided the most SSC, but grandmothers and aunts played an important role on the day of birth, while the mother was recovering from labour. One father participated in KMC and this infant had one of the highest mean daily durations of SSC. This finding must be interpreted with caution, as this infant was only observed for two days, but it presents an interesting argument for whether paternal involvement in KMC significantly affects the duration of SSC. Very little data regarding fathers and KMC exist from both low-income and high-income countries, and one of the key barriers to KMC adoption for men is lack of opportunity to practice (42). Men could have a significant direct impact on KMC initiation, by providing SSC themselves,

Table 3 Duration, timing and frequency of skin-to-skin contact (SSC) over first 7 days, by birthweight

Participant birthweight in grams	Mean daily hours of SSC (SD)	Age in hours at SSC initiation	Total number of SSC sessions
1200	2.8 (1.1)	20	9
1490	5.4 (1.6)	22.3	19
1500	2.6 (1.8)	26.5	9
1600	3.0 (2.4)	27.5	10
1680	4.0 (2.9)	5.5	15
1800	2.8 (2.0)	26.4	10
1800	1.9 (0.9)	44.5	7
2000	4.3 (1.5)	11.3	16
2000	0.9 (1.6)	20	3
2000	2.2 (1.5)	24.3	8
Sub-total	3.0 (2.1)		
Observed for less than 7 days			
1100 (2 days)	5.0 (2.8)	14.3	6
1800 (4 days)	2.0 (1.4)	17	5
Total	3.0 (2.1)	21.6 (12)	117

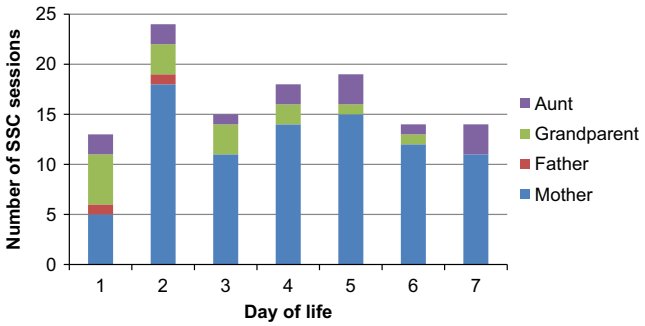

Figure 1 Various family members provided skin-to-skin contact (SSC) to low-birthweight infants over the first week of life.

and indirectly, by supporting the mother practically and emotionally (12).

STRENGTHS AND LIMITATIONS

The main strength of our study is that this was one of the few studies to examine KMC continuity and SSC in detail. Through direct observation, our study provided a description of numerous episodes of SSC at a low-resource facility in Uganda, where KMC is often poorly documented.

During the discussion of the study objectives and procedures, parents were provided with a brief description of KMC and its benefits. In some instances, they were hearing about KMC for the first time. Parents' awareness of the study objectives and the presence of an observer in the newborn unit could have had an impact on SSC practices, but the results do not suggest that these factors played a significant role.

The data collection tool was not piloted or tested prior to use, but the newborn unit paediatrician provided feedback during the protocol and tool development.

Another study of KMC (46) was occurring at the facility while our data were being collected for this study. The purpose, outcomes and data collected for these studies differed, but it is possible that one study may have influenced the other.

Studies evaluating routine KMC practice in resource-limited newborn units are scarce. Although the WHO endorses intermittent KMC, little is known about the dose–response relationship between the duration of SSC and clinical outcomes such as mortality, length of hospitalisation and feeding practices (3,9,11,42). More studies are needed to determine whether intermittent KMC, without conventional thermal care, confers the mortality impact described in a Cochrane Review (7). If a threshold for KMC is determined, recommendations could be more precise (42) and the demand placed on caregivers may be reduced (43).

CONCLUSION

Kangaroo mother care is a safe and effective way to decrease neonatal mortality, and there is increasing global attention being paid to KMC programmes. Our study found a disappointingly low daily duration of SSC and demonstrated that SSC was not practiced according to the current WHO recommendations in this Ugandan newborn unit. However, the nurses and midwives provided excellent education to caregivers on proper SSC techniques, as all the infants were positioned and clothed appropriately. While the mothers provided the most SSC, other family members, including one father, also participated. Further advocacy and community education on the care of preterm infants with SSC may help decrease the stigma of KMC, improve its overall acceptance and reduce the age at SSC initiation.

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CONFLICTS OF INTEREST

We have no conflict of interest to declare.

FINANCE

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A.3. Clinical cascades to assess physical readiness of facilities for the care of small and sick neonates in Kenya and Uganda. PLoS One 2018.

A.3.1. Copyright and permissions

A.3.2. Web appendix with supplementary tables and figures

The web appendix with supplementary tables and figures is available on the following pages.

A.3.2. Web appendix

S1 Table. Frequency and proportion of facilities with durable goods for neonatal care

Category	Item	2016 n (%)[a]	2017 n (%)[a]	Percentage point change	p-value[b]
Physical exam supplies	Thermometer	21 (91)	21 (91)	0	1.0000
	Stethoscope	15 (65)	21 (91)	26	0.0578
	Functional pulse oximeter with probe	10 (44)	5 (22)	-22	0.0588
	Tape measure	16 (70)	21 (91)	21	0.0956
	Newborn weighing scale	23 (100)	21 (91)	-9	0.1573
Testing and treatment supplies	Clean blade	22 (96)	19 (83)	-13	0.1797
	Clean cloth / towel (may be brought by mother)	12 (52)	4 (17)	-35	0.0325
	Resuscitation area with warmer / heat lamp	22 (96)	17 (74)	-22	0.0253
	Neonatal ventilation bag	18 (78)	15 (65)	-13	0.2568
	Mask – term or preterm size	15 (65)	17 (74)	9	0.5637
	Oxygen tubing	15 (65)	15 (65)	0	1.0000
	Suction device	21 (91)	20 (87)	-4	0.6547
	Glucometer	8 (35)	1 (4)	-31	0.0082
	Vitamin K (IM)	13 (57)	9 (39)	-18	0.2059
Equipment	Functional incubator or radiant warmer	19 (83)	15 (65)	-18	0.1025
	KMC beds or chairs	6 (26)	7 (30)	4	0.7055
	Filled oxygen cylinder or functional concentrator	18 (78)	18 (78)	0	1.0000
	Continuous positive airway pressure (CPAP) device	10 (44)	5 (22)	-22	0.0956
	Functional phototherapy unit	6 (26)	7 (30)	4	0.6547
Guidelines-assessment and treatment	Guidelines: referral of sick newborns	6 (26)	10 (44)	18	0.2059
	Neonatal resuscitation algorithm	7 (30)	15 (65)	35	0.0209
	Gestational age assessment tool	3 (13)	8 (35)	22	0.0588
	Preterm infant fluid / feeding guidelines	6 (26)	7 (30)	4	0.6547
	Guidelines: oxygen therapy	3 (13)	6 (26)	13	0.2568
	Guidelines: apnea of prematurity	1 (4)	9 (39)	35	0.0047
	Guidelines: treatment of neonatal sepsis	3 (13)	9 (39)	26	0.0339
	Guidelines: neonatal jaundice[c]				

[a] Data represent resource availability across all 23 health facilities at one time-point.

[b] Individual facilities were paired and p-values for resource availability by facility were calculated using McNemar's test.

[c] Presence of guidelines for neonatal jaundice was not assessed in this study.

S2 Table. Frequency and proportion of facilities with consumable supplies for neonatal care

Stage	Item	2016 n (%)[a]	2017 n (%)[a]	Percentage point change	p-value[b]
Examination and testing supplies	Water & soap (or hand disinfectant)	18 (78)	19 (83)	5	0.7055
	Disposable gloves	17 (74)	19 (83)	9	0.4142
	Lancets (neonatal or infant size)	13 (57)	11 (48)	-9	0.5271
	Glucose test strips	7 (30)	4 (17)	-13	0.2568
	Serum bilirubin measurement or bilirubin test strips[c]				
Medications	Tetracycline eye ointment	16 (70)	17 (74)	4	0.7055
	PMTCT in line with national policy[c]				
	Dextrose (IV)	22 (96)	18 (78)	-18	0.1025
	Ringers lactate or half normal saline/5% dextrose	21 (91)	21 (91)	0	1.0000
	Caffeine citrate or aminophylline	21 (91)	18 (78)	-13	0.2568
	Ampicillin or penicillin (IV)	20 (87)	14 (61)	-26	0.0578
	Gentamicin (IV)	18 (78)	17 (74)	-4	0.7389
	Ceftriaxone or cefotaxime (IV)	13 (57)	15 (65)	8	0.5271
	Phenobarbital (IV)[c]				
	Calcium gluconate (IV)	9 (39)	9 (39)	0	1.0000
Other treatment supplies	IV cannula sets (minimum size: 24 gauge)	17 (74)	15 (65)	-9	0.4795
	IV bags / tubing	6 (26)	4 (17)	-9	0.3173
	Nasogastric tube (neonatal size)	13 (57)	13 (57)	0	1.0000
	Syringes / feeding cups	19 (83)	20 (87)	4	0.6547
	Nasal cannula (neonatal size)	12 (52)	10 (44)	-8	0.5930

[a] Data represent resource availability across all 23 health facilities at one time-point.

[b] Individual facilities were paired and p-values for resource availability by facility were calculated using McNemar's test.

[c] Presence of these supplies and medications was not assessed in this study.

S3 Table. Neonatal care readiness in Kenyan and Ugandan health facilities by facility level, 2016 and 2017

Clinical cascade	Stage	Regional/district/ county level, n=5		Mission/PNFP level, n=4		Sub-county level, n=10		Health center level, n=4	
		2016 n (%)	2017 n (%)	2016 n (%)	2017 n (%)	2016 n (%)	2017 n (%)	2016 n (%)	2017 n (%)
Essential Newborn Care	Identify	5 (100)	4 (80)	3 (75)	4 (100)	6 (60)	9 (90)	4 (100)	2 (50)
	Treat	4 (80)	1 (20)	3 (75)	3 (75)	2 (20)	3 (30)	0	1 (25)
	Monitor-Modify	2 (40)	0	2 (50)	1 (25)	0	1 (10)	0	1 (25)
Neonatal Resuscitation	Identify	2 (40)	3 (60)	3 (75)	3 (75)	4 (40)	6 (60)	2 (50)	2 (50)
	Treat	2 (40)	2 (40)	2 (50)	2 (50)	3 (30)	3 (30)	0	1 (25)
	Monitor-Modify	1 (20)	1 (20)	1 (25)	0	0	0	0	0
Poor Feeding-Hypothermia	Identify	5 (100)	3 (60)	2 (50)	4 (100)	3 (30)	6 (60)	2 (50)	2 (50)
	Treat	2 (40)	1 (20)	0	0	0	0		
	Monitor-Modify	0	0	0	0	0	0	0[a]	2 (50)[a]
Respiratory Distress-Apnea	Identify	3 (60)	1 (20)	3 (75)	2 (50)	0	1 (10)	0	0
	Treat	2 (40)	0	2 (50)	2 (50)	0	0	0[b]	0[b]
	Monitor-Modify	0	0	0	0	0	0	0[a]	0[a]
Infection-Convulsions	Identify	3 (60)	4 (80)	3 (75)	3 (75)	3 (30)	8 (80)	3 (75)	2 (50)
	Treat	1 (20)	1 (20)	1 (25)	2 (50)	1 (10)	0	1 (25)[c]	1 (25)[c]
	Monitor-Modify	0	0	0	0	0	0	0[a]	1 (25)[a]
Jaundice	Identify	4 (80)	3 (60)	2 (50)	3 (75)	5 (50)	3 (30)	0	1 (25)
	Treat	2 (40)	1 (20)	0	3 (75)	1 (10)	1 (10)		
	Monitor-Modify	1 (20)	1 (20)	0	0	0	1 (10)	0[d]	1 (25)[d]

[a] Modified to include only guidelines for referral of sick newborns.

[b] Modified to include only mask, ventilation bag, and suction.

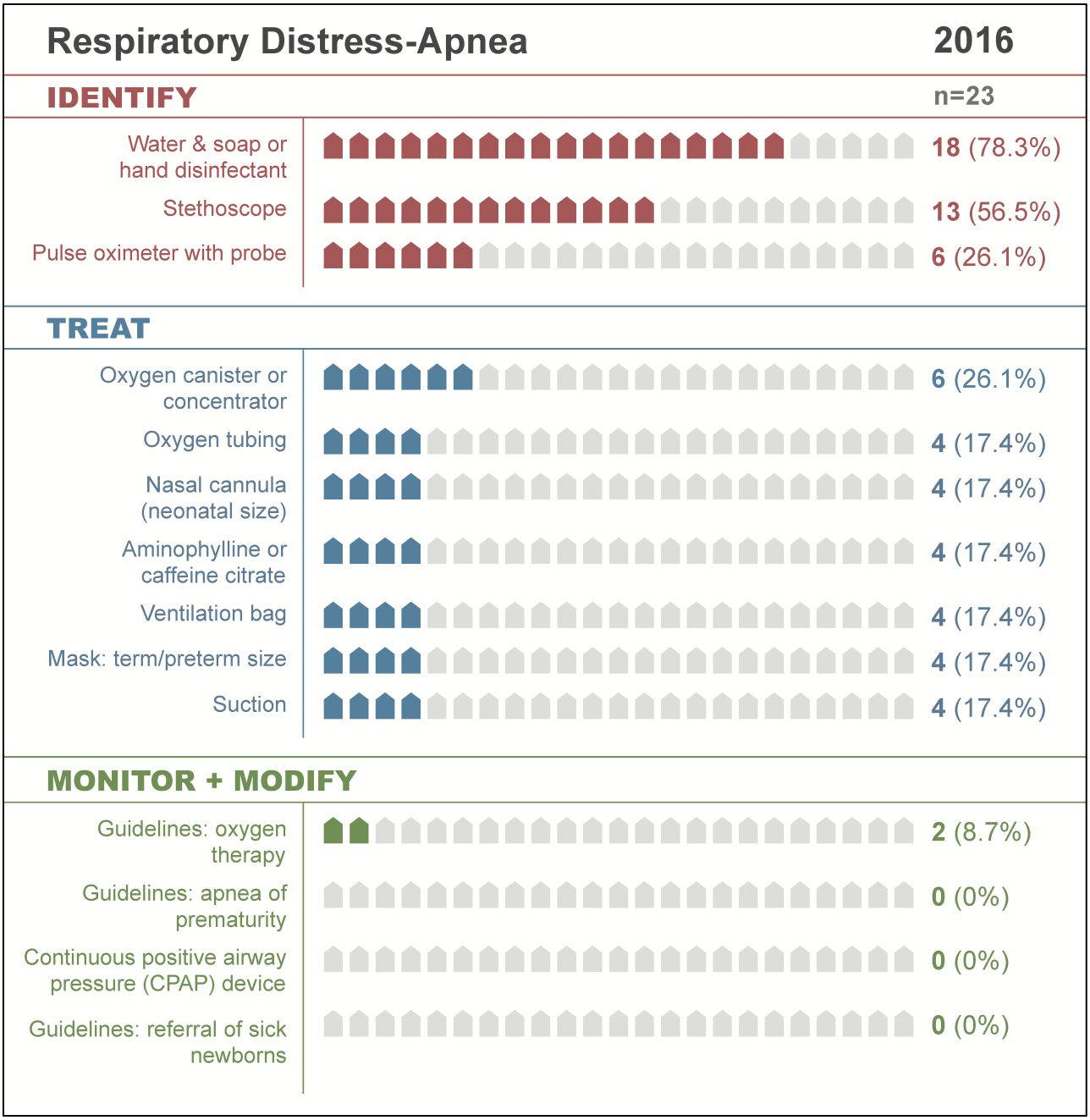
[c] Modified to include only newborn weighing scale, ampicillin (or penicillin) and gentamicin, with addition of sterile syringe and 23-25 gauge needle (for intramuscular injection)

[d] Modified to include only newborn weighing scale and guidelines for referral of sick newborns.

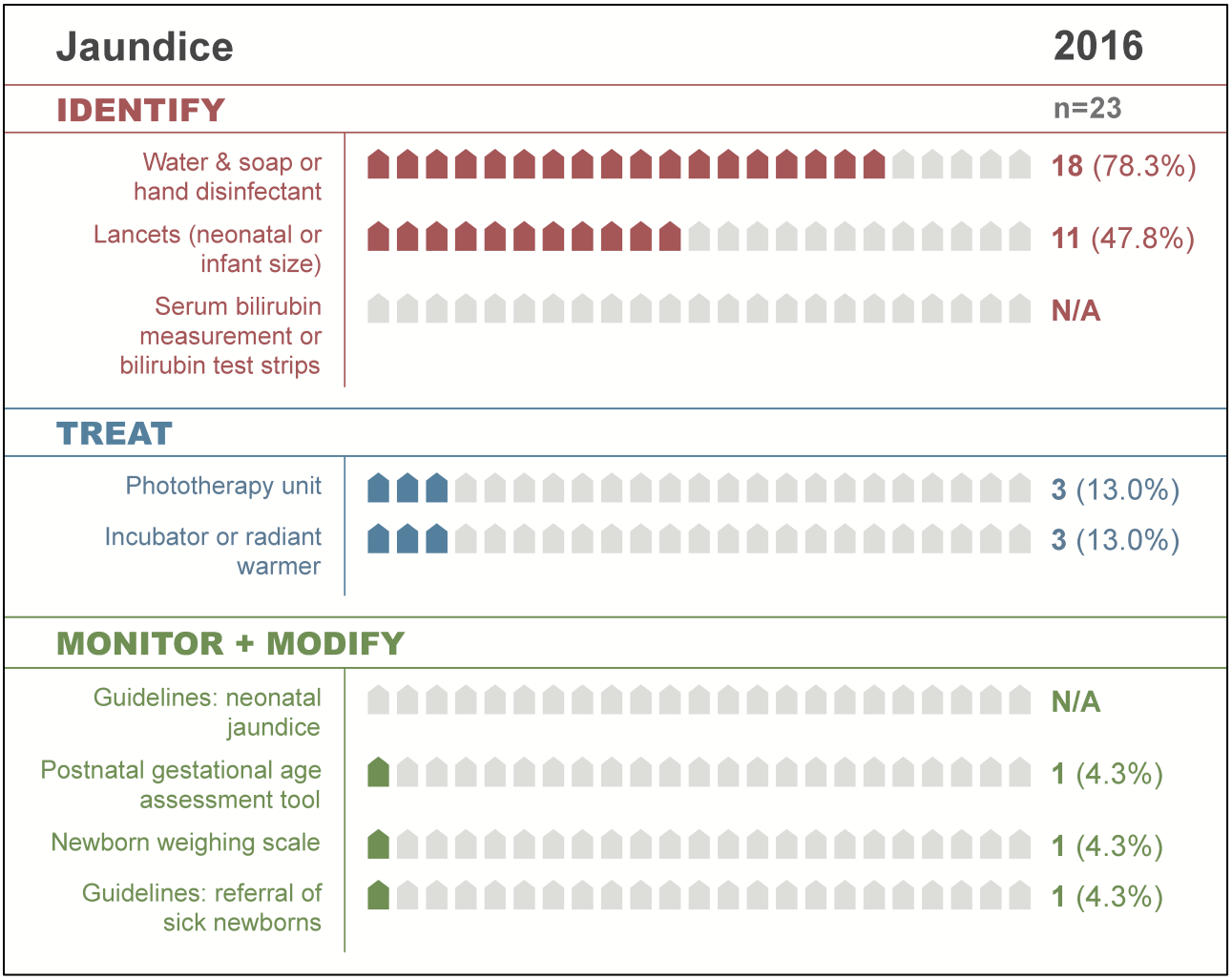
S4 Table. Neonatal care readiness in Kenyan and Ugandan health facilities by country, 2016 and 2017

Clinical cascade	Stage of care	Kenyan facilities, n=17		Ugandan facilities, n=6	
		2016 n (%)	2017 n (%)	2016 n (%)	2017 n (%)
Essential Newborn Care	Identify	13 (76)	14 (82)	5 (83)	5 (83)
	Treat	5 (29)	5 (29)	4 (67)	3 (50)
	Monitor-Modify	3 (18)	3 (18)	1 (17)	0
Neonatal Resuscitation	Identify	9 (53)	10 (59)	2 (33)	4 (67)
	Treat	6 (35)	4 (24)	1 (17)	4 (67)
	Monitor-Modify	2 (12)	0	0	1 (17)
Poor Feeding-Hypothermia	Identify	7 (41)	11 (65)	5 (83)	4 (67)
	Treat	0	0	2 (33)	1 (17)
	Monitor-Modify	0	0	0	0
Respiratory Distress-Apnea	Identify	3 (18)	1 (6)	3 (50)	3 (50)
	Treat	3 (18)	0	1 (17)	2 (33)
	Monitor-Modify	0	0	0	0
Infection-Convulsions	Identify	9 (53)	12 (71)	3 (50)	5 (83)
	Treat	1 (6)	0	2 (33)	3 (50)
	Monitor-Modify	0	0	0	0
Jaundice	Identify	7 (41)	5 (29)	4 (67)	5 (83)
	Treat	2 (12)	1 (6)	1 (17)	1 (17)
	Monitor-Modify	0	1 (6)	1 (17)	1 (17)

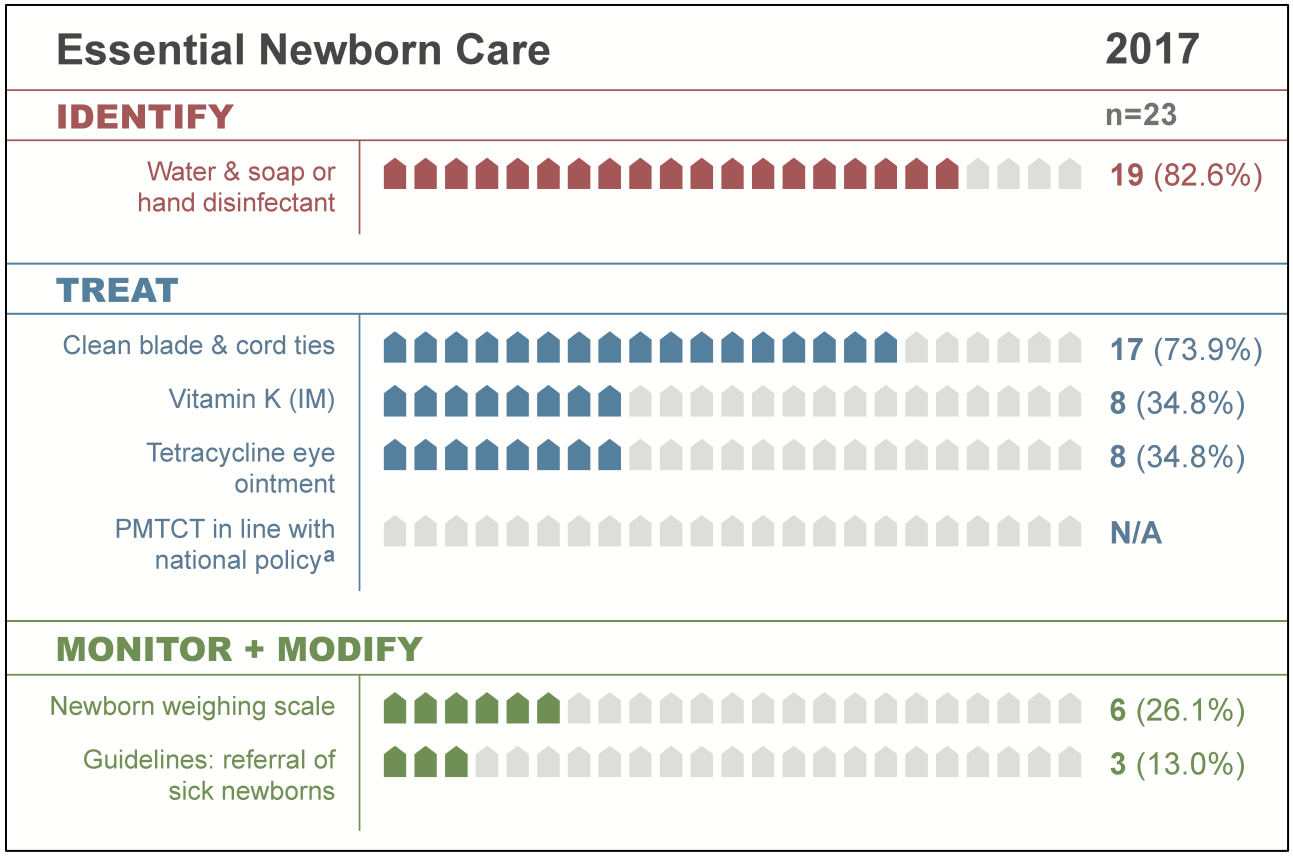
S1 Figure. Respiratory distress-apnea clinical cascade, 2016



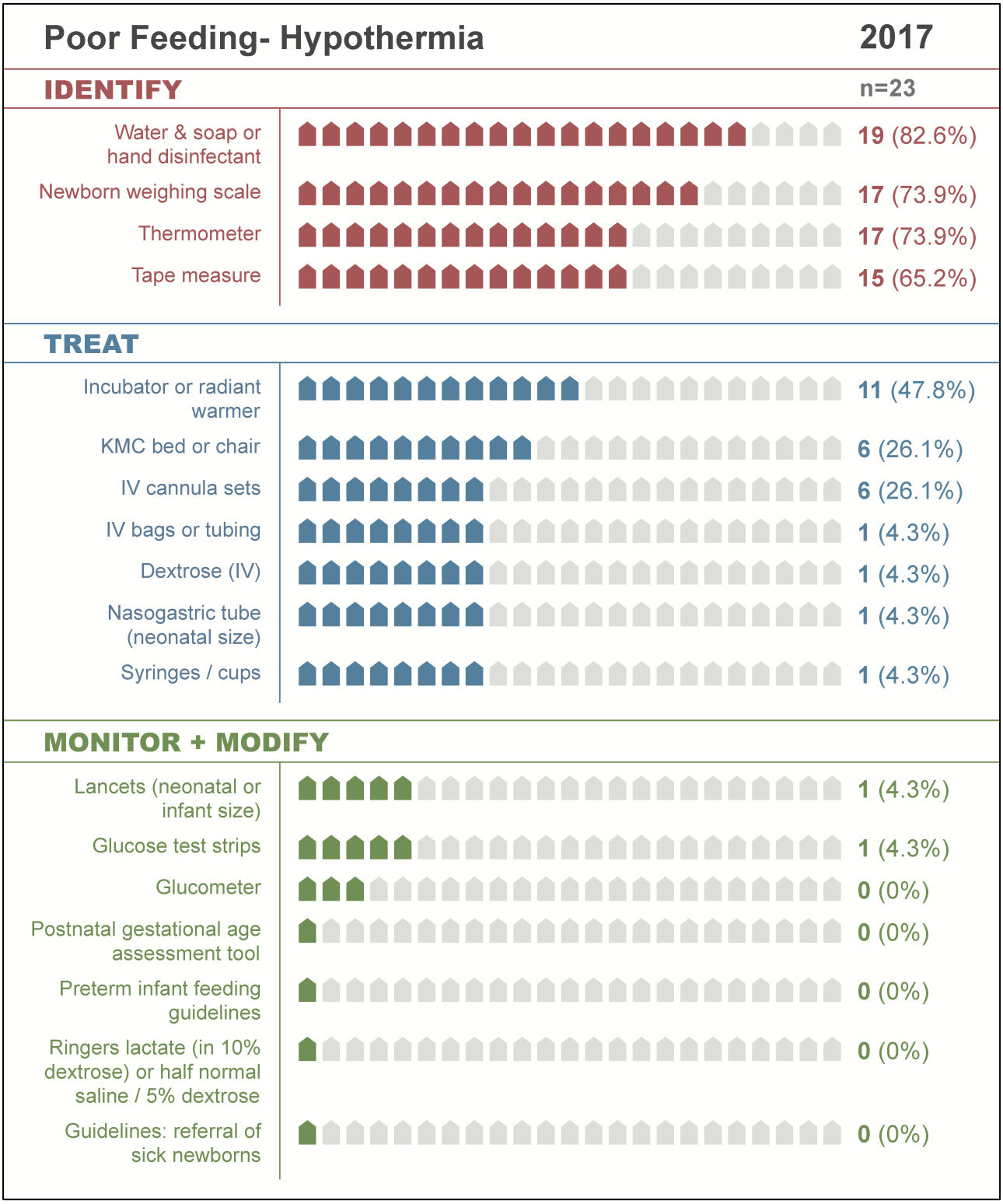
S2 Figure. Jaundice clinical cascade, 2016



S3 Figure. Essential newborn care clinical cascade, 2017



S4 Figure. Poor feeding-hypothermia clinical cascade, 2017



A.3.3. Ethical approvals

This work was covered within the broader research efforts of the UCSF Preterm Birth Initiative-East Africa, which received ethical approval from the Institutional Review Boards of UCSF, Makerere University, UNCST, and the Kenya Medical Research Institute. Letters of approval from UCSF, Makerere University, UNCST, and the Kenya Medical Research Institute are available on the following pages.

University of California
San Francisco

Human Research Protection Program
Institutional Review Board (IRB)

Expedited Review Approval

Principal Investigator: Dilys Walker, MD

Type of Submission: Submission Correction for Initial Review Submission Packet
Study Title: Strengthening selected interventions to improve birth outcomes and reduce morbidity and mortality of preterm infants in health facilities in Migori County, Kenya and Busoga Region, Uganda: An implementation science study

IRB #: 16-19162
Reference #: 161307

Committee of Record: San Francisco General Hospital Panel

Study Risk Assignment: Minimal

Approval Date: 03/29/2016 **Expiration Date:** 03/28/2017

This research satisfies the following condition(s) for the involvement of children:
45 CFR 46.404, 21 CFR 50.51: Research not involving greater than minimal risk.

Parental Permission and Assent:
The permission of one parent or guardian is sufficient.

The research meets all of the conditions of 45 CFR 46.204 for the involvement of pregnant women or fetuses.

The requirement for individual Research HIPAA Authorization is waived for some subjects, as detailed in the application. The use or disclosure of the requested information does not adversely affect the rights and welfare of the individuals and involves no more than a minimal risk to their privacy based on, at least, the presence of the following elements:

(1) an adequate plan to protect the identifiers from improper use and disclosure; (2) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or if such retention is otherwise required by law;
(3) adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule;
(4) the research could not practicably be conducted without the waiver; and (5) the research could not practicably be conducted without access to and use of the requested information.

A waiver of HIPAA Authorization and consent is acceptable for the recruitment procedures to identify potential subjects. The recruitment procedures involve routine review of medical or other records, do not adversely affect the rights and welfare of the individuals, and pose minimal risk to their privacy, based on, at least, the presence of the following elements:
(1) an adequate plan to protect the identifiers from improper use and disclosure; (2) an adequate plan to destroy

the identifiers at the earliest opportunity consistent with conduct of the research, or a health or research justification for retaining the identifiers was provided or such retention is otherwise required by law;
(3) adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule;
(4) the research could not practicably be conducted without the waiver; and (5) the study recruitment could not practicably be conducted without access to and use of the requested information. Study participants will sign a consent form prior to participation in the study.

A waiver of the requirement to obtain a signed consent form is acceptable for this study because, as detailed in the application, the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.
The waiver applies to some subjects, as detailed in the application.

A waiver or alteration of informed consent is acceptable because, as detailed in the application: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.
The waiver or alteration of informed consent applies to some subjects, as detailed in the application.

This submission was eligible for expedited review as:
Category 5: Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis)
Category 6: Collection of data from voice, video, digital, or image recordings made for research purposes
Category 7: Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies

All changes to a study must receive UCSF IRB approval before they are implemented. Follow the modification request instructions. The only exception to the requirement for prior UCSF IRB review and approval is when the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103.b.4, 21 CFR 56.108.a). In such cases, report the actions taken by following these instructions.

Expiration Notice: The iRIS system will generate an email notification eight weeks prior to the expiration of this study's approval. However, it is your responsibility to ensure that an application for continuing review approval has been submitted by the required time. In addition, you are required to submit a study closeout report at the completion of the project.

Documents Reviewed and Approved with this Submission (includes all versions – final approved versions are labeled 'Approved' in the Outcome column):

Consent Documents
Other Study Documents

For a list of all currently approved documents, follow these steps: Go to My Studies and open the study – Click on Informed Consent to obtain a list of approved consent documents and Other Study Documents for a list of other approved documents.

San Francisco Veterans Affairs Medical Center (SFVAMC): If the SFVAMC is engaged in this research, you must secure approval of the VA Research & Development Committee in addition to UCSF IRB approval and follow all applicable VA and other federal requirements. The UCSF IRB website has more information.

MAKERERE UNIVERSITY

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COLLEGE OF HEALTH SCIENCES
SCHOOL OF PUBLIC HEALTH
HIGHER DEGREES, RESEARCH AND ETHICS COMMITTEE

June 17th, 2016

Dr. Peter Waiswa
Principal Investigator, Protocol (395)
Makerere University, School of Public Health

Re: Approval of Proposal titled: Strengthening selected interventions to improve birth Outcomes and reduce morbidity and mortality of preterm infants in health facilities in Migori County, Kenya and Busoga Region, Uganda: An implementation science study

This is to inform you that, the Higher Degrees, Research and Ethics Committee (HDREC) has granted approval to the above referenced study, the HDREC reviewed the proposal during the 138th HDREC meeting held on April 12th, 2016 and provided suggestions and comments which you have adequately incorporated:

Please note that your study protocol number with HDREC is **395**. Please be sure to reference this number in any correspondence with HDREC. Note that the initial approval date for your proposal by HDREC is 17th/06/2016, and therefore approval expires at every annual anniversary of this approval date. The current approval is therefore valid until: **17th/06/2017**.

Continued approval is conditional upon your compliance with the following requirements:

1) No other consent form(s), questionnaire and/or advertisement documents should be used. The consent form(s) must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject must be given a copy of the signed consent form.

2) All protocol amendments and changes to other approved documents must be submitted to HDREC and not be implemented until approved by HDREC except where necessary to eliminate apparent immediate hazards to the study subjects.
3) Significant changes to the study site and significant deviations from the research protocol and all unanticipated problems that may involve risks or affect the safety or welfare of subjects or others, or that may affect the integrity of the research must be promptly reported to HDREC.
4) All deaths, life threatening problems or serious or unexpected adverse events, *whether related to the study or not,* must be reported to HDREC in a timely manner as specified in the National Guidelines for Research Involving Humans as Research Participants.

Makerere University School of Public Health • Higher Degrees, Research and Ethics Committee •
Valid Thru:
17 JUN 2017

- Please complete and submit reports to HDREC as follows:

a) For renewal of the study approval – complete and return the continuing Review Report – Renewal Request (Form 404A) at least 60 days prior to the expiration of the approval period. The study cannot continue until re-approved by HDREC.

b) Completion, termination, or if not renewing the project – send a final report within 90 days upon completion of the study.

- Finally, the legal requirement in Uganda is that all research activities must be registered with the National Council of Science and Technology. The forms for this registration can be obtained from their website www.uncst.go.ug. Please contact the Administrative Assistant of the Higher Degrees, Research and Ethics Committee at wtusiime@musph.ac.ug or telephone number (256)-393 291 397 if you encounter any problems.

Yours sincerely

[redacted]

Dr. Suzanne Kiwanuka

Chairperson: Higher Degrees, Research and Ethics Committee

Enclosures:

a) A stamped, approved study documents (informed consent documents):

Uganda National Council for Science and Technology

(Established by Act of Parliament of the Republic of Uganda)

Our Ref: HS 2076

6th December 2016

Dr. Peter Waiswa
School of Public Health
Makerere University
Kampala

Re: Research Approval: **Strengthening Selected Interventions to Improve Birth Outcomes and Reduce Morbidity and Mortality of Preterm Infants in Health Facilities in Migori County, Kenya and Busoga Region, Uganda: An Implementation Science Study**

I am pleased to inform you that on **27/06/2016**, the Uganda National Council for Science and Technology (UNCST) approved the above referenced research project. The Approval of the research project is for the period **27/06/2016** to **27/06/2017.**

Your research registration number with the UNCST is **HS 2076**. Please, cite this number in all your future correspondences with UNCST in respect of the above research project.

As Principal Investigator of the research project, you are responsible for fulfilling the following requirements of approval:

1. All co-investigators must be kept informed of the status of the research.
2. Changes, amendments, and addenda to the research protocol or the consent form (where applicable) must be submitted to the designated Research Ethics Committee (REC) or Lead Agency for re-review and approval **prior** to the activation of the changes. UNCST must be notified of the approved changes within five working days.
3. For clinical trials, all serious adverse events must be reported promptly to the designated local REC for review with copies to the National Drug Authority.
4. Unexpected events involving risks to research subjects/participants must be reported promptly to the UNCST. New information that becomes available which alters the risk/benefit ratio must be submitted promptly for UNCST review.
5. Only approved study procedures are to be implemented. The UNCST may conduct impromptu audits of all study records.
6. A progress report must be submitted electronically to UNCST within four weeks after every 12 months. Failure to do so may result in termination of the research project.

Below is a list of documents approved with this application:

	Document Title	Language	Version	Version Date
1.	Research Proposal	English	N/A	N/A
2.	PRONTO Consent Form (Video Analysis of Simulation data for Mentors and Mentees)	English	N/A	N/A
3.	PRONTO Consent Form (Live Birth Observation for Providers)			
4.	Follow Up Data Collection Tool	English	N/A	N/A

Yours sincerely,

[redacted]

Hellen N. Opolot
for: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

Copied to: Chair, Makerere University School of Public Health, Higher Degrees – Research Ethics Committee

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May 12, 2016

KEMRI/RES/7/3/1

TO: **DR. PHELGONA OTIENO,**
PRINCIPAL INVESTIGATOR

THROUGH: **DR. LEAH KIRUMBI,**
THE ACTING DIRECTOR, CCR,
NAIROBI

[redacted] 18/5/16

Dear Madam,

RE: **PROTOCOL NO. KEMRI/SERU/CCR/0034/3251 (*RESUBMITTED INITIAL SUBMISSION*): STRENGTHENING SELECTED INTERVENTIONS TO IMPROVE BIRTH OUTCOMES AND REDUCE MORBIDITY AND MORTALITY OF PRETERM BABIES IN HIGH VOLUME HEALTH FACILITES IN MIGORI COUNTY, KENYA: AN IMPLEMENTATION SCIENCE STUDY-(*VERSION 1.1 DATED MAY 2016*)**

Reference is made to your letter dated 5th May, 2016. KEMRI/Scientific and Ethics Review Unit (SERU) acknowledges receipt of the following revised study documents on 9th May, 2016:

1. Main protocol version 1.1 dated May 2016
2. Informed consent forms
   a. PRONTO written consent pre- and post-test for provider Version 1.1 dated May 2016.
   b. PRONTO written consent simulation provider Version 1.1 dated 1.1 May 2016
   c. PRONTO written consent live birth provider Version 1.1 dated 2016
   d. PRONTO written consent live birth mother (English) Version 1.1 dated May 2016
   e. Follow-up data collection consent (English) Version 1.1 dated May 2016
3. Follow-up telephone recruitment tool version 1.1 dated May 2016
4. Follow-up data collection tool version 1.1 dated May 2016

This is to inform you that the Committee notes that the issues raised during the 250th meeting of the KEMRI/Ethics Review Committee (ERC) held on 19th April, 2016 have been adequately addressed.

Consequently, the study is granted approval for implementation effective this day, **12th May, 2016** for a period of one year. Please note that authorization to conduct this study will automatically expire on **May 11, 2017.** If you plan to continue data collection or analysis beyond this date, please submit an application for continuation approval to SERU by **March 30, 2017**.

You are required to submit any proposed changes to this study to SERU for review and the changes should not be initiated until written approval from SERU is received. Please note that any unanticipated problems resulting from the implementation of this study should be brought to the attention of SERU and you should advise SERU when the study is completed or discontinued.

You may embark on the study.

Yours faithfully,

[redacted]

DR. EVANS AMUKOYE,
ACTING HEAD,
KEMRI/SCIENTIFIC AND ETHICS REVIEW UNIT

A.4. Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia. The Lancet Child and Adolescent Health 2020.

A.4.1. Copyright and permissions

A.4.2. Methods appendix with supplementary tables and figures

The methods appendix with supplementary tables and figures is available on the following pages.

A.4.2. Methods appendix

Methods appendix with supplementary tables and figures

Selection of candidate variables
Studies describing existing scoring systems for assessing neonatal mortality risk, illness severity, and clinical instability were reviewed to generate a list of potential parameters (Table S1). Parameters that are typically unavailable (e.g., oxygenation index), infrequently obtained (e.g., haematocrit), or unreliably measured (e.g., urine output) in low-resource settings were excluded (Table S2). Remaining parameters were evaluated using the following exclusion criteria: low prevalence in the NNRD (<0·1%); high prevalence of missing data in the development dataset (≥20%); not predictive of mortality in preterm or low birthweight neonates (e.g., thermoregulated environment); low prevalence within 24 hours (h) of birth (e.g., phototherapy); limited evidence to support validity (e.g., black race); concept better represented by an alternative variable (Table S2). Selection of candidate variables was conducted by members of the research team, which includes three neonatologists (one from US, two from UK), two of whom have extensive experience working in neonatal care in East Africa; a UK paediatrician based in The Gambia working in neonatal care; Gambian and Ugandan medical doctors with experience in neonatal care; and a UK paediatrician who is a global expert on newborn care and has an extensive background in neonatal care in LMICs, including throughout sub-Saharan Africa.

Study participants and data acquisition
UK samples
This study utilised data from 187 neonatal units in the UK National Neonatal Research Database (NNRD). The NNRD holds electronic patient-level data, recorded by health professionals as part of routine clinical care, from admissions to National Health Service (NHS) neonatal units in England from 2008, and Wales and Scotland from 2012. Data in the NNRD are de-identified and critical data items are fed back to and validated by treating clinicians. A formal comparison of NNRD data items against those recorded in case report forms of a randomised controlled trial demonstrated a high level of agreement (>95%).[1] Items in the National Neonatal Data Set are held within the NHS Data Dictionary.[2] This study included data on newborns admitted to neonatal units in England and Wales between January 2010 and December 2017.

The NNRD includes a total of approximately 140000 neonates born weighing ≤2000 grams (g) who were admitted to participating neonatal units in England and Wales from January 2010 to December 2017. For model development, 5 to 10 outcome events per predictor variable are required to obtain accurate and clinically useful results.[3] Using this guidance, the dataset was divided into the following samples:

- Development sample – all neonates ≤2000g admitted to a random sample of participating neonatal units in England and Wales from January 2010 to December 2016
- Random validation sample – all neonates ≤2000g admitted to the remaining participating neonatal units in England and Wales from January 2010 to December 2016
- Temporal validation sample – all neonates ≤2000g admitted to all neonatal units in England and Wales from January to December 2017

The following exclusion criteria were applied: birthweight >2000g; admitted at >6h of age or following discharge home; stillborn; died in the delivery room; moribund (received only comfort care prior to in-hospital death). Comfort care was defined as not receiving intubation, mechanical ventilation, vasopressors, or chest compressions.

Gambian sample
The Gambian validation sample included all neonates <2000g who were admitted to the neonatal unit at Edward Francis Small Teaching Hospital in Banjul between May 2018 and September 2019, and who were screened but not enrolled in the 'Early KMC' (eKMC) trial (NCT03555981).

Routine data, including mode of delivery and treatments administered during the first 24h post-birth, were collected from routine medical charts and recorded in an Excel spreadsheet by trained study personnel. Other routine and non-routine data, collected as part of the eKMC trial screening process, were exported from the trial database and transferred to the spreadsheet. These data included birthweight, sex, birth plurality (singleton or multiple), referral status (inborn or outborn), and oxygen saturation (SpO_2) at admission (%). Due to the stepwise nature of the eKMC screening process, SpO_2 was not required for those neonates who were deemed ineligible. Accordingly, if a neonate's SPO_2 measurement was not recorded in the trial database, study personnel attempted to collect this data from routine medical charts.

Outcome measure
The primary outcome was in-hospital mortality. Mortality has been utilised as the outcome against which most neonatal intensive care risk scores have been designed and validated.[4,5,14,6–13] Mortality is clearly and directly related to illness severity, objectively measured, and reliably ascertainable.[9]

Missing data
Missing data were excluded from the analysis for continuous variables. In this study, categorical variables include therapy-based risk factors (e.g., IV fluids) and clinical signs that are non-continuous (e.g., convulsions). Recording the absence of categorical variables is not mandatory in the data sources from which the NNRD is extracted; thus, these fields are often left blank to indicate absence. Therefore, there are several reasons why a neonate may not have such a variable recorded.[15] First is the possibility that the neonate was healthy and, thus, did not require the therapy or have the clinical sign. This is the assumption that was made in the development of this score; the same assumption was made in the development of the widely used SNAP and CRIB scores. The second possibility is that the therapy was given or the clinical sign was present, but this information was not documented in the medical record. Given that a comparison of NNRD data items against those recorded for a randomised trial demonstrated >95% agreement,[1] this was considered to be unlikely. Other possibilities include that the clinician should have ordered the therapy or noted the clinical sign, but failed to do so as a result of inadequate knowledge or skill. This was thought to be unlikely in UK neonatal units, which are staffed by neonatologists and/or paediatricians experienced in neonatal care. The data sources from which the NNRD data are drawn are summary data describing the treatments received or the signs detected on a particular day; therefore, treatments 'ordered' but not administered will not be recorded and, thus, will not be included in the NNRD. This was confirmed in the aforementioned NNRD validation study.[1]

Model development
Continuous data were presented using means and standard deviations (SD) for parametric data and medians and interquartile ranges (IQR) for non-parametric data. Categorical data were presented as counts and proportions. Logistic regression models were derived to model the risk of in-hospital mortality. Robust standard errors were used to allow for clustering within neonatal units. All candidate variables were included in a complete multivariable model, which was progressively simplified using reverse stepwise selection, with the least statistically significant variable being removed at each step. Model discrimination was assessed with the c-index,[16] equivalent to the area under the receiver operating characteristic curve, which ranges from 0·5 (no predictive ability) to 1 (perfect discrimination).[17] Overall goodness-of-fit was assessed with the Brier score, which ranges from 0 (perfect fit) to a maximum value dependent upon outcome incidence (0·25 for 50% incidence).[18,19] Calibration was evaluated using graphical plots of observed versus predicted risk; perfect predictions lie on the 45 degree line.[19] Locally weighted scatterplot smoothing was used to estimate the relationship between observed and predicted probabilities.[20] A sensitivity analysis excluding neonates whose admission age was uncertain (anonymised data derived from calculated difference between time of birth and time of admission) was conducted to reassess performance, as admission at >6h of birth was an exclusion criterion. Model performance was additionally reassessed following exclusion of neonates who were transferred for any reason since outcome data were not available for these babies. Performance for predicting mortality within 24h of birth was evaluated in a secondary analysis, as 36% of neonatal deaths globally occur within this timeframe.[21]

Multiple imputation
Methods
We employed multiple imputation (MI) with chained equations to impute missing values for incomplete predictor variables in the development sample. The imputation model included the primary outcome, predictor variables, and candidate variables believed to be associated with missing data values and/or patterns of missingness. Candidate variables were added in a stepwise process to assess model convergence and compatibility; those resulting in convergence failure were excluded. Stata version 15 was used to perform all imputation analyses (*mi impute chained, mi estimate*). Continuous variables were imputed using predictive mean matching (k=10) due to non-normality and restricted range; categorical variables were imputed using logistic regression.[22] Variables were analysed in sequence from the most observed to the least observed. Fifteen imputed datasets were generated, with 10 iterations per dataset. The logistic regression model was executed across the 15 datasets and results were combined to create a single set of inferential statistics, using Rubin's rules.[23] MI estimates of the β coefficients and c-index were compared to original estimates. Monte Carlo errors were examined to assess statistical reproducibility.[23]

Results
Following imputation of missing values for incomplete predictor variables (n=54956), β coefficient estimates were nearly identical to original estimates (Table S3), thus no adjustments were made to the model coefficients. Discriminatory performance of the model was unchanged, with a c-index of 0·8894 (95% CI: 0·8818-0·8969). Estimates of Monte Carlo errors for β coefficients, standard errors, and p-values suggested that the MI process could be statistically reproduced. The average relative variance increase was 0·0457 and the largest fraction of missing information was 0·0902.

Risk score development
We assigned the parameters in the final model points proportional to their β regression coefficient values.[24–26] Whole numbers were used in order to generate an easily calculable score.

Logistic regression equation relating the risk model to in-hospital mortality:

$$\text{Log odds of mortality} = 2.6142 - (0.0032*\text{birthweight}) + (0.3167*\text{nasal cannula/headbox}) + (1.6214*\text{CPAP/mechanical ventilation}) - (0.0390*\text{admission } SpO_2)$$

Logistic regression equation relating the risk score to in-hospital mortality:

$$\text{Log odds of mortality} = 0.1901 - (0.3256*\text{NMR-2000})$$

A risk score was calculated for each patient and predictive margins with 95% confidence intervals (CI) were computed across a broad range of risk score percentiles (Table S4). Using these margins as a guide, the development sample was arbitrarily divided into three groups: neonates at low risk, medium risk, and high risk for mortality. To assess the calibration of the integer score to the model using regression coefficients, observed risks in risk groups and population deciles of the risk score were derived and compared with the mean predicted risks in each group or population decile (Figure S1). We assessed overall predictive ability of the integer score using the c-index.

Internal validation

Internal validity refers to the reproducibility of a risk prediction model for the underlying population from which the data originated.[27] Bootstrap resampling, with 1000 samples within the development sample, was used to internally validate the final model at the two time-points and to estimate optimism-adjusted measures of model discrimination and overall fit in each bootstrap sample.[28] Overfitting is a phenomenon whereby the process of generating a model that has optimal fit for the development dataset results in reduced fit when the model is applied to other datasets and, thus, provides an optimistic evaluation of its predictive ability.[29] Performance of the refitted model in each bootstrap sample was compared to that of the refitted model in the original development sample. Estimates of optimism for the c-index and Brier score were averaged and subtracted to provide optimism-adjusted measures.

External validation

External validity refers to the generalisability of a model's performance to related populations.[27] The final model was evaluated in three external validation samples, each selected to assess distinctive features of performance. The random validation sample, drawn from the neonatal units withheld from the development sample, tested the performance of the model when applied to different neonatal care settings in the UK within the same timeframe. The temporal validation sample, drawn from all units in the development and random validation samples during the final twelve months of data collection, tested performance in the same neonatal units over time. The Gambian sample tested performance in a LMIC neonatal care setting. We assessed model performance in each validation sample separately and in the UK full (combined) validation sample. Discrimination and overall goodness-of-fit were evaluated using the c-index and Brier score, respectively. Calibration was assessed using graphical plots of observed versus predicted risk. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated across a wide range of possible cut-points in the UK development and full validation samples (Table S5).

We assessed overall performance of the simplified integer score using the c-index and Brier score in all external validation samples (Table S6). In the Gambian sample, we re-defined low-, medium-, and high-risk groups to account for increased case fatality in this setting. To assess the calibration of the integer score to the model using regression coefficients, observed risks in groups and population deciles of risk scores were derived and compared with mean predicted risks in each group or population decile of the Gambian sample (Figure S2). A risk score was calculated for each neonate and predictive margins with 95% CIs were computed across a broad range of score percentiles (Table S7). Using these margins as a guide, the Gambian sample was arbitrarily divided into three groups: neonates at low-, medium-, and high-risk for mortality.

Comparison with the CRIB-II score

The Clinical Risk Index for Babies (CRIB, CRIB-II),[5,8] the Score for Neonatal Acute Physiology (SNAP, SNAP-II),[6,9] and the SNAP Perinatal Extension (SNAPPE, SNAPPE-II)[7,9] are the most widely used neonatal intensive care risk scores. The Transport Risk Index of Physiologic Stability (TRIPS, TRIPS-II) is a related physiology-based approach that can be assessed at any point within the first 24h and repeated as a baby's clinical condition changes.[13,14] The NNRD did not include all of the variables required for calculation of CRIB, SNAP, SNAP-II, SNAPPE-II, TRIPS, or TRIPS-II (Table S2); hence, CRIB-II was selected for comparison. CRIB-II includes 5 variables (sex, birthweight, gestational age, temperature, base excess), all collected within 1h of admission.[8] As CRIB-II has only been validated for use in neonates up to 32 weeks gestational age, we compared the c-index and Brier score for CRIB-II and NMR-2000 amongst neonates ≤32 weeks in the full validation sample. All statistical analyses for this study were completed using Stata version 15 (College Station, Texas, United States).

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Table S1. Characteristics of development studies reviewed to generate list of potential parameters

	Model	Approach	Dates	Setting	Sample size[a]	In-hospital mortality[a]
Gray, 1992[4]	NTISS[b]	Therapy-based	1989-90	3 NICU[c], USA	1768	114
Horbar, 1993[30]	NICHHD[d]	Perinatal factors	1987-89	7 NICU[c], USA	3603	890
International Neonatal Network, 1993[5]	CRIB[e]	Physiology-based + perinatal factors	1988-90	4 NICU[c], UK	812	201
Richardson, 1993[6]	SNAP[f]	Physiology-based	1989-90	3 NICU[c], USA	1643	114
Richardson, 1993[7]	SNAPPE[g]	Physiology-based + perinatal factors	1989-90	3 NICU[c], USA	1089	59
Maier, 1997[31]	Unnamed	Physiology-based + perinatal factors + 1 therapy measure	1978-87	1 NICU[c], Germany	396	106
Fischer, 1998[32]	SCRIP[h]	Physiology-based	Not reported	1 NICU[c], Germany	20	Not reported
Richardson, 2001[9]	SNAP-II[f], SNAPPE-II[g]	Physiology-based (SNAP) + perinatal factors (SNAPPE)	1996-97	17 NICU[c], Canada	10819	418
Lee, 2001[13]	TRIPS[i]	Physiology-based	1996-97	8 NICU[c], Canada (transport service)	1115	Not reported
Parry, 2003[8]	CRIB-II[e]	Physiology-based + perinatal factors	1998-99	54 NICU[c], UK	3027	240
Broughton, 2004[11]	MINT[j]	Physiology-based + perinatal factors	1992-2001	Neonatal transport service in Australia	1252	138
Zupancic, 2007[10]	VON-RA[k]	Physiology-based + perinatal factors	2002	>500 NICU[c], Vermont Oxford Network	10439	1072
Rosenberg, 2008[33]	SAWS[l]	Perinatal factors	1998-2003	2 NICU[c], Egypt and Bangladesh	428[j]	262
Lee, 2013[14]	TRIPS-II[i]	Physiology-based	2006-08	15 NICU[c], Canada	11383	411
Sutcuoglu, 2015[12]	TREMS[m]	Physiology-based	2011	1 NICU[c], Turkey (transport service)	306	56
Shah, 2015[34]	Unnamed	Therapy-based + perinatal factors	2010-12	23 NICU[c], Canada	9978	650
Rathod, 2016[35]	SNS[n]	Physiology-based	2012-13	1 NICU[c], India (transport service)	303	60
Morgan, 2018[36]	Unnamed	Therapy-based	2015-16	1 neonatal unit (regional referral hospital), Uganda	264[o]	2[o]

[a] Total sample size and number of in-hospital deaths in the development cohort.
[b] Neonatal Therapeutic Intervention Scoring System (NTISS)
[c] Neonatal intensive care unit (NICU)
[d] National Institute of Child Health and Human Development (NICHHD)
[e] Clinical Risk Index for Babies (CRIB, CRIB-II)
[f] Score for Neonatal Acute Physiology (SNAP, SNAP-II)
[g] Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE, SNAPPE-II)
[h] Stability of the Cardio-Respiratory System in Premature Infants (SCRIP)
[i] Transport Risk Index of Physiologic Stability (TRIPS, TRIPS-II)
[j] Mortality Index for Neonatal Transportation (MINT)
[k] Vermont Oxford Network-Risk Adjustment (VON-RA)
[l] Simplified age-weight-sex (SAWS); sample comprised of neonates enrolled in clinical trials of topical emollient therapy at two tertiary care hospitals (one in Egypt, one in Bangladesh).
[m] Transport Related Mortality Score (TREMS)
[n] Sick Neonate Score (SNS)
[o] Sample comprised of 254 neonates in a retrospective audit and 10 in a prospective study evaluating the feasibility of kangaroo mother care for clinically unstable neonates; in-hospital mortality is reported for the feasibility study.

Table S2. Parameters evaluated for potential inclusion in the modelling process

	Model(s)	Inclusion/exclusion
Perinatal factors	NA[a]	NA[a]
Birthweight	CRIB[b], SNAPPE-II[c], CRIB-II[b], MINT[d], SAWS[e], NICHHD[f], Maier[g]	Included
Gestational age	CRIB, CRIB-II[b], SAWS[e], VON-RA[h]	Included
Sex	CRIB-II[b], SAWS[e], NICHHD[f], VON-RA[h]	Included
Postnatal age	MINT[d]	Excluded- only validated as a binary risk factor (0-1 vs. >1 hour) among neonates transported within 72 hours (h)[11]
Small-for-gestational age	SNAPPE-II[c], NICHHD[f]	Included
Apgar score at 1 minute	MINT[d], NICHHD[f], VON-RA[h]	Excluded- often unavailable in LMIC facilities, especially for babies born at home or transferred from another facility
Apgar score <7 at 5 minutes, Apgar score at 5 minutes	SNAPPE-II[c], Maier[g], VON-RA[h]	Excluded- as above
Congenital anomaly[i]	CRIB[b], MINT[d], VON-RA[h]	Unreliable diagnosis in LMIC settings- modified to 'presence of visually recognisable anomaly at birth' using a predefined list of conditions
Black race	NICHHD[f]	Excluded- limited evidence; only validated in 1 study (published in 1993)
Outborn status	VON-RA[h]	Excluded- only validated in combination with SNAP-II[10]
Multiple gestation	VON-RA[h]	Excluded- as above
Caesarean delivery	VON-RA[h]	Excluded- as above, plus not available in many LMIC facilities
Therapy-based	NA[a]	NA[a]
Cardiopulmonary resuscitation in first 24h	NTISS[j]	Modified to 'bag-mask resuscitation at time of delivery'
Surfactant administration in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Oxygen therapy in first 24/48h	NTISS[j], KMC[k]	Included as 'oxygen therapy within 24h of birth'
Continuous positive airway pressure in first 24/48h	NTISS[j], KMC[k]	Modified to 'highest level of respiratory support within 24h of birth'
Mechanical/high frequency ventilation in first 24h, at admission	NTISS[j], Maier[g]	Excluded- better represented by alternative variable ('highest level of respiratory support within 24h of birth')
Tracheostomy in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Extracorporeal membrane oxygenation in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Endotracheal intubation in first 24h	NTISS[j]	Excluded- better represented by alternative variable ('highest level of respiratory support within 24h of birth'), low data completeness in NNRD
PaO_2/FiO_2 ratio in first 12/24h	SNAP-II/SNAP[l]	Excluded- not included in NNRD, infeasible for LMIC settings
Oxygenation index in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for LMIC settings
Minimum/maximum FiO_2 in first 12h	CRIB[b]	Excluded- not included in NNRD, infeasible for LMIC settings
Indomethacin administration in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Vasopressor administration in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Pacemaker therapy in first 24h	NTISS[j]	Excluded- not included in NNRD, infeasible for LMIC settings
Antibiotic therapy in first 24/48h	NTISS[j], KMC[k]	Included as 'antibiotic therapy within 24h of birth'
Diuretic therapy in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Steroid administration in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Anticonvulsant therapy in first 24/48h	NTISS[j], KMC[k]	Included as 'anticonvulsant therapy within 24h of birth'
Caffeine (or aminophylline) in first 24/48h	NTISS[j], KMC[k]	Included as 'caffeine or aminophylline within 24h of birth'
Treatment of metabolic acidosis in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Potassium binding resin administration in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Frequent vital signs/cardiorespiratory monitoring in first 24h	NTISS[j]	Excluded- unreliable, infeasible for LMIC settings
Frequent phlebotomy in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Thermoregulated environment in first 24h	NTISS[j]	Excluded- not useful to predict mortality risk amongst neonates ≤2000g, as all require some form of thermal support (KMC, incubator, or radiant warmer)
Arterial, central venous pressure monitoring in first 24h	NTISS[j]	Excluded- not included in NNRD, infeasible for LMIC settings
Urinary catheter in first 24 hours	NTISS[j]	Excluded- not included in NNRD, infeasible for LMIC settings
Gavage feeding	NTISS[j]	Excluded- not useful to predict mortality risk amongst neonates ≤2000g, as those born at <35 weeks may require gavage feeding until coordinated suck and swallow develops (typically around 32 to 34 weeks)

Intravenous (IV) amino acid administration, IV potassium infusion within first 24h	NTISS[j]	Modified to 'IV fluids within 24h of birth'
IV fluids within 48h of birth	KMC[k]	Excluded- better represented by alternative variable ('IV fluids within 24h of birth')
Insulin administration in first 24h	NTISS[j]	Excluded- low prevalence, infeasible for LMIC settings
Phototherapy in first 24/48h	NTISS[j], KMC[k]	Excluded- low prevalence within 24h of birth
Blood product transfusion in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Exchange transfusion in first 24h	NTISS[j]	Excluded- infeasible for LMIC settings
Patient transport in first 24h	NTISS[j]	Excluded- infeasible in many LMIC settings
Chest tube in first 24h	NTISS[j]	Excluded- low prevalence in NNRD, infeasible for LMIC settings
Pericardial tube in first 24h	NTISS[j]	Excluded- low prevalence in NNRD, infeasible for LMIC settings
Operation in first 24h	NTISS[j]	Excluded- low prevalence in NNRD, infeasible for LMIC settings
Thoracentesis in first 24h	NTISS[j]	Excluded- low prevalence in NNRD, infeasible for LMIC settings
Pericardiocentesis in first 24h	NTISS[j]	Excluded- low prevalence in NNRD, infeasible for LMIC settings
Dialysis in first 24h	NTISS[j]	Excluded- low prevalence in NNRD, infeasible for LMIC settings
Vascular access in first 24h[m]	NTISS[j]	Excluded- low prevalence in NNRD, arterial and central venous access infeasible for LMIC settings
Clinical signs/observations	NA[a]	NA[a]
Blood pressure in first 12/24h, at admission	SNAP-II/SNAP[l], TRIPS, TRIPS-II[n], TREMS[o], SNS[p]	Excluded- high proportion of missing data (30·3%) in development set
Heart rate in first 24h, at admission	SNAP[l], MINT[d], SNS[p]	Included as 'Heart rate at admission'
Respiratory rate in first 24h, at admission	SNAP[l], SNS[p]	Modified to 'Respiratory rate at admission'
Temperature at admission (within first hour)	CRIB-II[b], TREMS[o], TRIPS, TRIPS-II[n], SNS[p]	Included as 'temperature at admission'
Temperature in first 12/24h	SNAP-II/SNAP[l]	Excluded- better represented by alternative variable ('temperature at admission')
Oxygen saturation in first 24h, at admission	NTISS[j], TREMS[o], SNS[p]	Included as 'Oxygen saturation at admission'
Urine output in first 12/24h, quantitative intake and output in first 24h	SNAP-II/SNAP[l], NTISS[j]	Excluded- unreliable measure, infeasible for LMIC settings
Number of seizures in first 12/24h	SNAP-II/SNAP[l]	Number not included in NNRD- modified to 'any seizures within 24h of birth'
Apnoeic episodes in first 24h	SNAP[l]	Unreliable measure in present form- modified to 'clinically relevant increase in apnoea/bradycardia episodes, oxygen requirement, or ventilatory support'
Respiratory status/effort, severity of respiratory distress at admission	TRIPS, TRIPS-II[n], Maier[g], SNS[p]	Excluded- better represented by alternative variables ('RR at admission,' 'SpO_2 at admission' 'clinically relevant increase in apnoea/bradycardia episodes, oxygen requirement, ventilatory support, or respiratory rate')
Response to noxious stimuli	TRIPS, TRIPS-II[n]	Excluded- not included in NNRD
Capillary refill time at admission	SNS[p]	Excluded- prevalence <0.1% in NNRD
Episodes of apnoea, bradycardia, or oxygen desaturation measured over 5-minute periods 13 times throughout the first 6h	SCRIP[q]	Excluded- infeasible for routine clinical use; better represented by alternative variable ('clinically relevant increase in apnoea/bradycardia episodes, oxygen requirement, ventilatory support, or respiratory rate')
Laboratory measures	NA[a]	NA[a]
Serum pH in first 12/24h, at admission	SNAP-II/SNAP[l], MINT[d]	Excluded- infeasible for routine use in LMIC settings
PaO_2 in first 24h, at admission	SNAP[l], MINT[d]	Excluded- not included in NNRD, infeasible for LMIC settings
pCO_2 in first 24h, at admission	SNAP[l], TREMS[o]	Excluded- infeasible for routine use in LMIC settings
Base excess in first 12h, within 1h, on admission	CRIB, CRIB-II[b], Maier[g]	Excluded- infeasible for routine use in LMIC settings
Haematocrit in first 24h	SNAP[l]	Excluded- not included in NNRD
White blood cell count in first 24h	SNAP[l]	Excluded- not included in NNRD
Immature total ratio in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for LMIC settings
Absolute neutrophil count in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for LMIC settings
Platelet count in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for routine use in LMIC settings
Blood urea nitrogen in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for routine use in LMIC settings
Creatinine in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for routine use in LMIC settings
Bilirubin in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for routine use in LMIC settings

Sodium in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for routine use in LMIC settings
Potassium in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for routine use in LMIC settings
Calcium in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for routine use in LMIC settings
Blood glucose in first 24h, on admission	SNAP[l], TREMS[o], SNS[p]	Excluded- high proportion of missing data (23·9%) in development set
Serum bicarbonate in first 24h	SNAP[l]	Excluded- not included in NNRD, infeasible for routine use in LMIC settings
Stool guaiac in first 24h	SNAP[l]	Excluded- not included in NNRD

[a] Not applicable (NA).
[b] Clinical Risk Index for Babies (CRIB, CRIB-II).
[c] Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE, SNAPPE-II).
[d] Mortality Index for Neonatal Transportation (MINT).
[e] Simplified age-weight-sex (SAWS).
[f] National Institute of Child Health and Human Development (NICHHD).
[g] Unnamed mortality risk score for VLBW neonates, published by Maier et al.
[h] Vermont Oxford Network-Risk Adjustment (VON-RA).
[i] The CRIB score stratified the risk of congenital anomalies into 3 categories: 1) none; 2) non-acutely life threatening; 3) acutely life threatening.[5] The MINT score categorized this variable solely by its presence or absence, as recorded at the time of the referral call.[11] The VON-RA score defined congenital anomalies using a predefined list of conditions.[37]
[j] Neonatal Therapeutic Intervention Scoring System (NTISS).
[k] Therapy-based clinical instability criterion used in study exploring KMC feasibility amongst unstable neonates in Uganda.[36]
[l] Score for Neonatal Acute Physiology (SNAP, SNAP-II).
[m] The NTISS defined vascular access to include peripheral IV, arterial, and central venous lines, with higher therapeutic intensity weights assigned to arterial and central venous access (subscore: 2) than peripheral IV access (subscore: 1).[4]
[n] Transport Risk Index of Physiologic Stability (TRIPS, TRIPS-II).
[o] Transport Related Mortality Score (TREMS).
[p] Sick Neonate Score (SNS).
[q] Stability of the Cardio-Respiratory System in Premature Infants (SCRIP).

Table S3. NMR-2000 logistic model following multiple imputation versus original estimates in development sample

	Multiple imputation (n=54956)		Original estimates (n=46108)	
	β Coefficient	**95% Confidence interval**	**β Coefficient**	**95% Confidence interval**
Birthweight	-0.0032	-.0035 to -.00289[a]	-0·0032	-0·0035 to -0·0029[a]
Highest respiratory support within first 24h	··, NA[b]	··, NA[b]	··, NA[b]	··, NA[b]
Nasal cannula or headbox	0.3896	0.0014 to 0.7778[c]	0·3167	-0·1055 to 0·7389[a]
CPAP, Bi/SiPAP, or invasive ventilation	1.4977	1.1909 to 1.8045[a]	1·6214	1·2682 to 1·9746[a]
SpO_2 at admission (%)	-0.0386	-0.0449 to -0.0322[a]	-0·0390	-0·0455 to -0·0326[a]
Constant	2.8229	1.9410 to 3.7047[a]	2·6142[f]	1·7655 to 3·4629[a]

[a] Estimate significant to p-value <0·0001.
[b] Not applicable.
[c] Estimate significant to p-value <0·05.

Table S4. Predicted mortality risk across score percentiles in the development sample (n=46108)

Percentile	Score	Mean predicted mortality risk[a]	95% Confidence interval[a]
1%	3·9	34·1	29·1 - 39·0
5%	6·1	18·5	15·6 - 21·4
10%	7·9	11·1	9·3 - 12·8
25%	12·0	4·7	3·9 - 5·4
50%	17·2	1·1	0·9 - 1·3
75%	21·1	0·2	0·2 - 0·3
90%	22·9	0·1	0·06 - 0·1

[a] All predictions significant to p-value <0.0001.

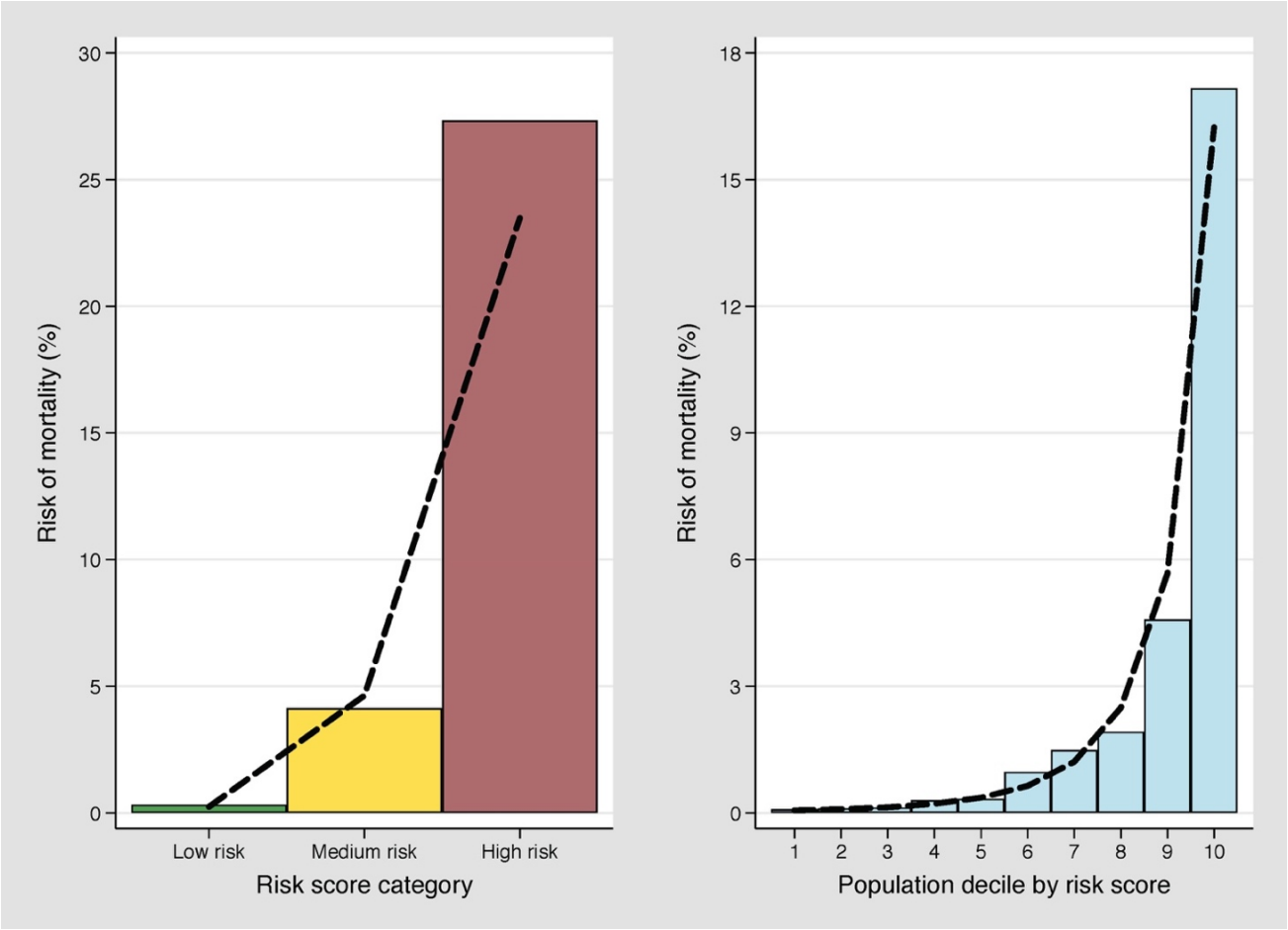

Figure S1. Predicted versus observed risk of death for pre-defined categories and population deciles by risk score in the development sample (n=46108). Predicted risk of death derived from exact regression model (dotted lines) versus observed risk of death (solid bars).

Table S5. Sensitivity and specificity based on predicted mortality risk in the development (n=46108) and full validation samples (n=47846)

	Sensitivity (95% CI)	Specificity (95% CI)	PPV[a] (95% CI)	NPV[b] (95% CI)
Development	NA[c]	NA[c]	NA[c]	NA[c]
0·5%	96·1 (94·8-97·1)	52·9 (52·4-53·3)	5·4 (5·1-5·7)	99·8 (99·7-99·8)
1%	91·9 (90·2-93·4)	64·4 (63·9-64·8)	6·7 (6·3-7·1)	99·7 (99·6-99·7)
3·9%[d]	79·1 (76·7-81·3)	82·9 (82·5-83·2)	11·4 (10·7-12·1)	99·3 (99·2-99·4)
5%	75·3 (72·8-77·7)	85·7 (85·4-86·0)	12·8 (12·0-13·5)	99·2 (99·1-99·3)
10%	60·1 (57·4-62·9)	93·1 (92·9-93·3)	19·5 (18·2-20·8)	98·8 (98·7-98·9)
20%	26·1 (23·7-28·7)	98·4 (98·3-98·5)	31·3 (28·5-34·3)	98·0 (97·8-98·1)
Full validation	NA[c]	NA[c]	NA[c]	NA[c]
0·5%	96·5 (95·5-97·4)	52·0 (51·5-52·4)	6·1 (5·8-6·4)	99·8 (99·7-99·8)
1%	91·7 (90·2-93·1)	63·4 (63·0-63·9)	7·5 (7·1-7·9)	99·6 (99·5-99·7)
3·9%[d]	81·6 (79·6-83·6)	81·0 (80·7-81·4)	12·2 (11·6-12·9)	99·3 (99·2-99·4)
5%	78·4 (76·2-80·4)	83·9 (83·5-84·2)	13·6 (12·9-14·4)	99·2 (99·1-99·3)
10%	65·6 (63·1-68·0)	91·3 (91·1-91·6)	19·7 (18·6-20·9)	98·8 (98·7-98·9)
20%	34·6 (32·2-37·1)	97·7 (97·6-97·8)	32·8 (30·5-35·2)	97·9 (97·7-98·0)

[a] Positive predictive value (PPV).
[b] Negative predictive value (NPV).
[c] Not applicable (NA).
[d] Empirical optimal cutpoint based on the Youden Index.[38]

Table S6. Risk score performance in the external validation samples

	Random validation n=35193	Temporal validation n=12653	Full validation n=47846	Gambian validation n=457
Brier score	0·0272	0·0237	0·0263	0·1715
C-index	0·8910	0·8872	0·8903	0·8082

Table S7. Predicted mortality risk across score percentiles in the Gambian validation sample (n=457)

Percentile	Score	Mean predicted mortality risk[a]	95% Confidence interval[a]
1%	4·2	96·8	94·0 - 99·6
5%	7·0	92·5	88·3 - 96·7
10%	9·0	89·2	84·3 - 94·2
25%	12·5	73·8	67·3 - 80·4
50%	17·0	48·1	42·7 - 53·5
75%	20·0	25·3	20·3 - 30·2
90%	22·0	14·5	10·0 - 18·9

[a] All predictions significant to p-value <0.0001.

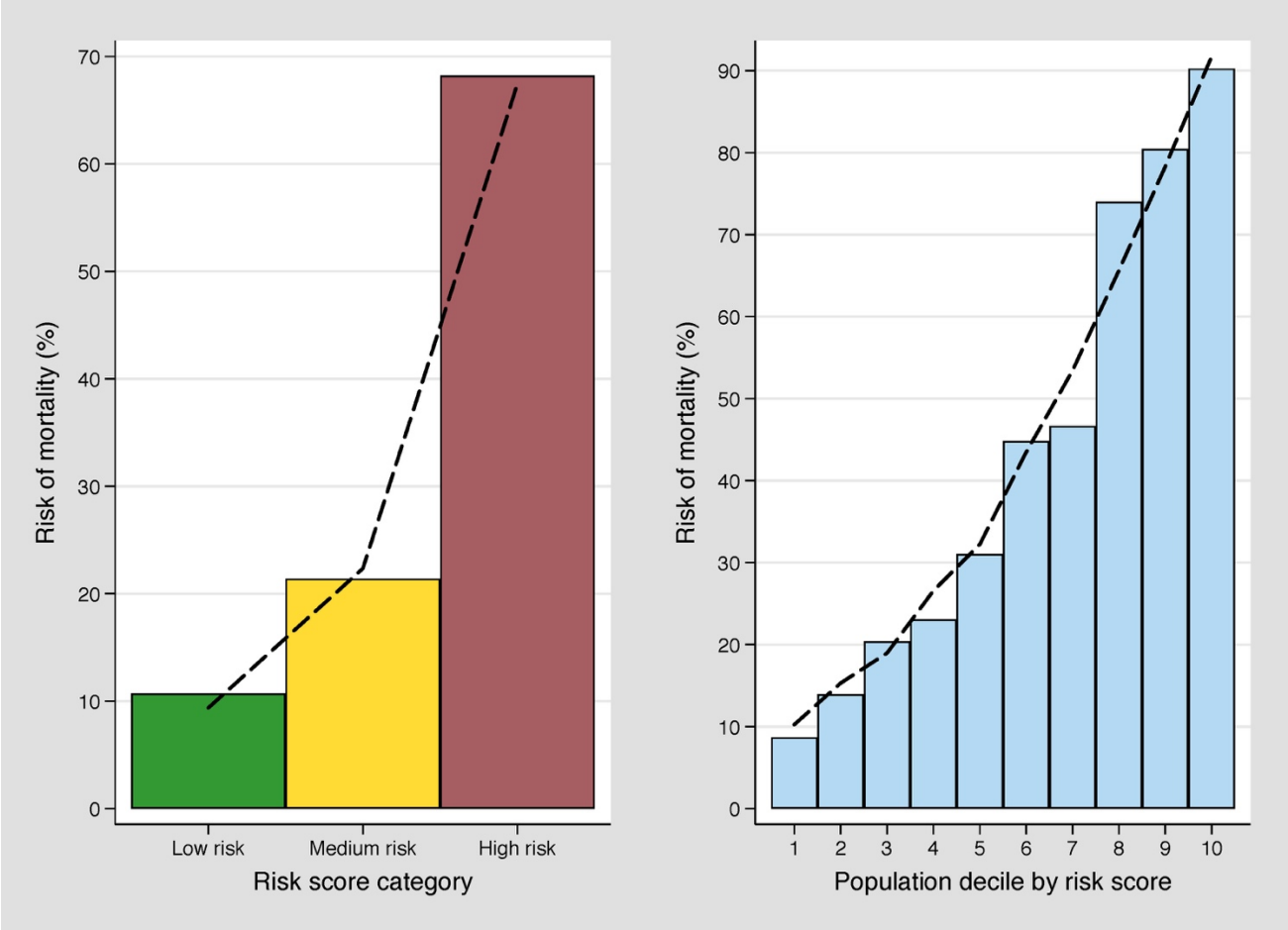

Figure S2. Predicted versus observed risk of death for pre-defined categories and population deciles by risk score in the Gambian validation sample (n=457). Predicted risk of death derived from exact regression model (dotted lines) versus observed risk of death (solid bars).

A.4.3. Ethical approvals

Model development and validation in the UK was approved by the UK Health Research Authority and the Research Ethics Committees (REC) of North West–Preston (17/NW/0709) and LSHTM (#14594). The Gambian validation study was approved by RECs of the Gambian Government/Medical Research Council (MRC) Unit The Gambia at LSHTM (#1643) and LSHTM (#16189). Letters of approval from LSHTM, North West–Preston, the UK Health Research Authority, and the Gambian Government/MRC Unit The Gambia are available on the following pages.

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Observational / Interventions Research Ethics Committee

Dr Melissa Morgan
LSHTM

14 February 2018

Dear Dr Morgan

Study Title: The OMWaNA Study: Operationalising kangaroo Mother care among unstable low birth Weight Neonates in Africa: Developing and validating a clinical stability index to help providers determine eligibility

LSHTM Ethics Ref: 14594

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Local Approval	Chris Gale - NDAU Board Approval email	19/10/2017	1.0
Local Approval	238074 17.NW.0709 favourable opinion 30.11.2017	11/11/2017	1.0
Protocol / Proposal	OMWaNA study_NDAUprotocol_v3	15/11/2017	3.0
Local Approval	LSHTM Sponsorship Letter_QA1081_MMorgan_20.11.17	20/11/2017	1.0
Local Approval	238074; 17NW0709 - Letter of HRA Approval - 14.12.2017	14/12/2017	1.0
Investigator CV	Morgan CV_Jan 2018_UK	29/01/2018	1.0
Investigator CV	Cally Tann_CV	29/01/2018	1.0
Investigator CV	Joy Lawn CV 2018	29/01/2018	1.0
Investigator CV	Diana Elbourne_CV	29/01/2018	1.0
Investigator CV	Peter Waiswa_CV	29/01/2018	1.0
Investigator CV	Elizabeth Allen_CV	29/01/2018	1.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]
Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

North West - Preston Research Ethics Committee
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4 Minshull Street
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Telephone: 020 71048008

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

30 November 2017

Dr Melissa Morgan
Keppel Street
London
WC1E 7HT

Dear Dr Morgan

Study title:	**The OMWaNA Study: Operationalising kangaroo Mother care among unstable low birth Weight Neonates in Africa: Developing and validating a clinical stability index to help providers determine eligibility**
REC reference:	**17/NW/0709**
Protocol number:	**QA1079**
IRAS project ID:	**238074**

The Proportionate Review Sub-committee of the North West - Preston Research Ethics Committee reviewed the above application in correspondence.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Summary of discussion at the meeting (if applicable)

The members had no ethical issues with this application.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
IRAS Application Form [IRAS_Form_28112017]		28 November 2017
IRAS Application Form XML file [IRAS_Form_28112017]		28 November 2017
Research protocol or project proposal	3	15 November 2017
Summary CV for Chief Investigator (CI)		
Summary CV for supervisor (student research)		
Summary CV for supervisor (student research)		

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

<u>Reporting requirements</u>

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

17/NW/0709	**Please quote this number on all correspondence**

Yours sincerely

Dr Rob Monks
Chair

Email: nrescommittee.northwest-preston@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers"

Copy to: *Mrs Patricia Henley*
Dr Essam Ramhamadany, Chelsea and Westminster NHS Foundation Trust

NHS
Health Research Authority

Dr Melissa Morgan
Keppel Street
London
WC1E 7HT

Email: hra.approval@nhs.net

14 December 2017

Dear Dr Morgan

Letter of HRA Approval

Study title:	**The OMWaNA Study: Operationalising kangaroo Mother care among unstable low birth Weight Neonates in Africa: Developing and validating a clinical stability index to help providers determine eligibility**
IRAS project ID:	**238074**
Protocol number:	**QA1079**
REC reference:	**17/NW/0709**
Sponsor	**London School of Hygiene & Tropical Medicine**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from the HRA website.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found through IRAS.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please use the feedback form available on the HRA website.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details on the HRA website.

Your IRAS project ID is **238074**. Please quote this on all correspondence.

Yours sincerely

Maeve Ip Groot Bluemink
Assessor

Email: hra.approval@nhs.net

Copy to: *Mrs Patricia Henley, London School of Hygiene & Tropical Medicine – Sponsor Contact*

Dr Essam Ramhamadany, Chelsea and Westminster NHS Foundation Trust – Lead R&D Contact & Participating NHS organisations in England

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		20 November 2017
HRA Statement of Activities	1 (HRA final)	14 December 2017
IRAS Application Form [IRAS_Form_28112017]		28 November 2017
Other [data sharing agreement]		
Research protocol or project proposal	3	15 November 2017
Summary CV for Chief Investigator (CI)		
Summary CV for supervisor (student research) [Joy Lawn]		
Summary CV for supervisor (student research) [Elizabeth Allen]		

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Observational / Interventions Research Ethics Committee

Dr Helen Brotherton
LSHTM

10 January 2019

Dear Helen,

Study Title: Developing and validating a mortality risk score for neonates weighing less than 2000 grams to help providers determine eligibility for kangaroo mother care in low-resource settings

LSHTM ethics ref: 16189

Thank you for your application for the above research, which has now been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	Neonatal clinical stability scoring system_NDAUprotocol_v3	15/11/2017	3
Investigator CV	CV HB June 2018	01/06/2018	1.0
Investigator CV	Morgan CV_Oct2018_UK	01/10/2018	1.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

The Gambia Government/MRCG Joint
ETHICS COMMITTEE

C/o MRC Unit: The Gambia @ LSHTM, Fajara
P.O. Box 273, Banjul
The Gambia, West Africa
Fax: +220 – 4495919 or 4496513
Tel: +220 – 4495442-6 Ext. 2308
Email: ethics@mrc.gm

21 January 2019

Ms. Melissa Morgan,
London School of Hygiene & Tropical Medicine, UK /
University of California San Francisco, USA

Dear Ms. Morgan,

SCC 1643v1.2, Developing And Validating A Mortality Risk Score For Neonates Weighing Less Than 2000 Grams To Help Providers Determine Eligibility For Kangaroo Mother Care In Low-resource Settings

Thank you for submitting your response letter dated 13 January 2019 addressing the issue raised by the Gambia Government/MRCG Joint Ethics Committee at its meeting held on 18 December 2018.

Your application has now received the full approval of our committee and may proceed.

With best wishes,

Yours sincerely,

[redacted]

Dr. Mohammadou Kabir Cham
Chair, Gambia Government/MRCG Joint Ethics Committee

Documents submitted for review:

- Response letter – 13 January 2018
- SCC approval letter – 4 December 2018
- Response letter – 4 December 2018
- Request letter to EFSTH – 4 December 2018
- SCC application form, version 1.2 – 15 January 2019

A.4.4. Accompanying Comment in The Lancet Child and Adolescent Health

A.4.4.1. Citation

Lee SK, Zhou Q. Neonatal risk adjustment in low-resource settings. *Lancet Child Adolesc Health* 2020; 4: 256-257. doi: 10.1016/S2352-4642(20)30039-0.

A.4.4.2. Copyright and permissions

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	131393	**Title**	Dr
First Name(s)	Melissa Morgan		
Surname/Family Name	Medvedev		
Thesis Title	Informing the design of a trial of kangaroo mother care initiated before stabilisation amongst small and sick newborns in a sub-Saharan African context using mixed methods		
Primary Supervisor	Elizabeth Allen		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	The Lancet Child and Adolescent Health as: Lee SK, Zhou Q. Neonatal risk adjustment in low-resource settings. Lancet Child Adolesc Health 2020; 4: 256-257. doi: 10.1016/S2352-4642(20)30039-0.		
When was the work published?	28 February 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	Not applicable		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	

Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	This is a Comment piece that accompanied the NMR-2000 risk score paper (Chapter 4); both were published in The Lancet Child and Adolescent Health in February 2020. The linked Comment was authored by Shoo Lee and Qi Zhou; I played no role in its preparation. The Comment is included as a supplementary annex (A.4.4).

SECTION E

Student Signature	Melissa Medvedev
Date	3 August 2020

Supervisor Signature	Elizabeth Allen
Date	05/08/2020

Neonatal risk adjustment in low-resource settings

Mauro Fermariello/Science Photo Library

Lancet Child Adolesc Health 2020

Published Online
February 28, 2020
https://doi.org/10.1016/S2352-4642(20)30039-0

See Online/Articles
https://doi.org/10.1016/S2352-4642(20)30021-3

Risk adjustment is the process of sorting patients into different risk groups to permit fair comparisons of outcomes.[1] This is important because although randomisation in clinical trials evenly distributes risk among the comparison groups, this is not possible when comparing real-world outcomes among different hospitals or groups of patients. Consequently, risk adjustment is an indispensable tool for real-world comparisons of outcomes. These comparisons are essential for quality improvement because they permit valid examination of variations in outcomes. If particular practices are associated with unusually good or poor outcomes, then clinical trials can be done to find out which treatments are the cause. Many therapies are used on the basis of experience rather than randomised clinical trials, and effectiveness might differ when applied to different populations and combined with untested therapies. Thus, field effectiveness is as important to evaluate as experimental efficacy, and risk adjustment is an indispensable tool for comparative effectiveness studies, collaborative quality improvement, and policy research.

Most risk adjustment instruments use a combination of variables that measure biological risks (eg, respiratory distress syndrome, congenital anomalies), vulnerability (eg, birthweight), or that are proxies for other risks (eg, socioeconomic status), and the selection of variables is determined by the desired outcome. For neonatal mortality, several well validated and widely used risk adjustment scores exist, including Clinical Risk Index for Babies (CRIBS), Score for Neonatal Acute Physiology version II (SNAP-II), Neonatal Therapeutic Intervention Scoring System (NTISS), Transport Risk Index of Physiologic Stability version II (TRIPS-II), and the Simplified Age-Weight-Sex (SAWS).[2–6] So, why produce another neonatal risk adjustment score? Melissa Medvedev and colleagues[7] rightly point out that existing neonatal risk adjustment scores were mostly created for use in high-resource settings and require data that are not easy to collect in low-resource settings, which limits their usability. SAWS is an exception in that it was designed specifically for low-resource settings, but this score has been reported to have only moderate discrimination for in-hospital mortality.[6] Medvedev and colleagues' new score, NMR-2000, is intended to fill this gap and to provide low-resource settings with a tool that can facilitate efforts in benchmarking, quality improvement, and research. This laudable goal might spur quality improvement efforts in low-resource settings that could lead to substantial system-wide improvements and better patient outcomes, as has been amply shown by existing networks in high-resource settings, such as the Vermont-Oxford Neonatal Network, California Perinatal Quality Care Collaborative, and the Canadian Neonatal Network.[8–10]

Medvedev and colleagues[7] used retrospective, observational data from the large UK National Neonatal Research Database (187 neonatal units) to derive the NMR-2000 score by including only variables that were considered easily available in low-resource settings. They then validated the score using data from the database (more than 55 000 neonates admitted to any unit between Jan 1, 2010 and Dec 31, 2017) and data from a Gambian cohort (550 neonates weighing less than 2000 g who were admitted to the Edward Francis Small Teaching Hospital, Banjul, The Gambia, between May 1, 2018, and Sept 30, 2019). Their approach is innovative because low-resource settings are often restricted by an absence of large cohorts with reliable data. The results showing that NMR-2000 compares favourably with other neonatal risk adjustment scores for prediction of mortality in both the UK (c-index of 0·8859–0·8930 and a Brier score of 0·0232–0·0271) and Gambian cohorts (c-index of 0·8170 and a Brier score of 0·1688) is heartening. However, it is perhaps not surprising, because the three variables selected were birthweight, admission oxygen saturation, and highest level of respiratory support during the first 24 h of admission.[7] Birthweight is the single most predictive variable of neonatal mortality, and respiratory status is the most common source of neonatal physiological instability. What is surprising is the choice of oxygen saturation as an eligible variable because many hospitals in low-resource settings might have no ready access to oxygen saturation monitors, which limits the usefulness of the NMR-2000. The TRIPS-II score might be more practical because it uses clinical observations that are easy to make without the need for instrumentation.[5] Additionally, because NMR-2000

uses measurements made over 24 h, interventions during the initial 24 h can influence the outcome and bias the results, whereas TRIPS-II is measured almost instantly, and can be used sequentially so that mortality risks can be revised as the condition of the infant changes. However, the TRIPS-II has not been validated in low-resource settings.

Medvedev and colleagues[7] should be commended because NMR-2000 might stimulate benchmarking and collaborative quality improvement efforts in countries where outcome improvements are badly needed at affordable costs, and the effect could be substantial. Indeed, such efforts should be encouraged and funding made available. However, it should be remembered that risk prediction models come with important caveats. Quality of care should consider not only mortality, but also factors such as morbidity, quality of life, access to care, and cost of care. In addition, even when risk prediction models based on routinely collected health data work well for populations, they do not reliably predict individual risks and should not be applied to individuals.

We declare no competing interests.

*Shoo K Lee, Qi Zhou
shoo.lee@sinaihealth.ca

Departments of Pediatrics, Obstetrics and Gynecology, and Public Health, University of Toronto, Toronto, ON, Canada (SKL); Department of Pediatrics, Mount Sinai Hospital, Toronto, ON, Canada (SKL, QZ); Department of Neonatology, Children's Hospital of Fudan University, Shanghai, China (QZ)

1 Richardson D, Tarnow-Mordi WO, Lee SK. Risk adjustment for quality improvement. *Pediatrics* 1999; **103** (suppl E)**:** 255–65.
2 The International Neonatal Network. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. *Lancet* 1993; **342:** 193–98.
3 Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. *J Pediatr* 2001; **138:** 92–100.
4 Gray JE, Richardson DK, McCormick MC, Workman-Daniels K, Goldmann DA. Neonatal therapeutic intervention scoring system: a therapy-based severity-of-illness index. *Pediatrics* 1992; **90:** 561–67.
5 Lee SK, Aziz K, Dunn M, et al. Transport Risk Index of Physiologic Stability, version II (TRIPS-II): a simple and practical neonatal illness severity score. *Am J Perinatol* 2013; **30:** 395–400.
6 Rosenberg RE, Ahmed S, Saha SK, et al. Simplified age-weight mortality risk classification for very low birth weight infants in low-resource settings. *J Pediatr* 2008; **153:** 519–24.
7 Medvedev MM, Brotherton H, Gai A, et al. Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia. *Lancet Child Adolesc Health* 2020; published online Feb 28. https://doi.org/10.1016/S2352-4642(20)30021-3.
8 Horbar JD. The Vermont Oxford Network: evidence-based quality improvement for neonatology. *Pediatrics* 1999; **103** (suppl E)**:** 350–59.
9 Gould JB. The role of regional collaboratives: the California Perinatal Quality Care Collaborative model. *Clin Perinatol* 2010; **37:** 71–86.
10 Lee SK, Beltempo M, McMillan DD, et al. Outcomes and care practices for preterm infants born at less than 33 weeks' gestation: a quality-improvement study. *CMAJ* 2020; **192:** e81–91.

A.5. Search strategy for literature review of randomised controlled trials examining the effect of KMC on mortality, length of stay, and hypothermia

I searched PubMed for studies published from inception through October 31, 2016 using the following search terms. Equivalent dates and search terms were used for EMBASE and Google Scholar. Only relevant articles were retrieved.

Kangaroo care

(kangaroo-mother care method[MeSH] OR kangaroo mother care OR kangaroo care OR skin-to-skin care OR skin-to-skin contact)

AND

Newborn

(infant, newborn[MeSH] OR newborn OR new-born OR neonate OR neonatal OR infant, premature/ OR infant, preterm/ OR infant, low birth weight/ OR LBW OR infant, very low birth weight/ OR VLBW OR infant, extremely low birth weight/ OR ELBW OR infan* OR neonat*)

AND

Randomised controlled trial

(randomised controlled trial OR controlled clinical trial OR clinical trials as topic[MeSH] OR Clinical Trial[ptyp] OR randomised[tiab] OR [tiab] OR trial[ti]).

To identify relevant ongoing trials, I searched the following databases most recently in October 2019 using the terms, "kangaroo care" and "skin-to-skin contact."

- Australian and New Zealand Clinical Trials Registry: www.anzctr.org.au
- European Union Clinical Trials Register: www.clinicaltrialsregister.eu
- US National Institutes of Health Clinical Trials Registry: www.clinicaltrials.gov
- WHO International Clinical Trials Registry platform: www.who.int/trialsearch

A.6. Kangaroo Mother Care for clinically unstable neonates: is it feasible at a hospital in Uganda? Journal of Global Health 2018.

A.6.1. Copyright and permissions

A.6.2. Ethical approvals

Ethical approval was obtained from the Institutional Review Boards at LSHTM, Makerere University, and UNCST. Letters of approval from LSHTM, Makerere University, and UNCST are available on the following pages.

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Observational / Interventions Research Ethics Committee

Dr Melissa Morgan
LSHTM

9 May 2016

Dear Melissa

Study Title: The OMWaNA Study: Feasibility and acceptability of an individually randomised trial of kangaroo mother care for clinically unstable infants weighing ≤2000g in Uganda

LSHTM Ethics Ref: 10597

Thank you for responding to the Interventions Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	Morgan CV Jan 2016_UK	28/01/2016	1.0
Investigator CV	Harriet Nambuya_CV	28/01/2016	1.0
Investigator CV	Peter Waiswa_CV	28/01/2016	1.0
Investigator CV	Joy Lawn CV	28/01/2016	1.0
Investigator CV	Elizabeth Allen CV	28/01/2016	1.0
Investigator CV	Janet Seeley CV	28/01/2016	1.0
Investigator CV	Mike English CV	28/01/2016	1.0
Investigator CV	Cally Tann CV	28/01/2016	1.0
Protocol / Proposal	OMWaNA Study Feasibility and Acceptability Protocol_v3_3May2016	03/05/2016	3.0
Information Sheet	Feasibility Part 2 Consent Form_v2_3May 2016	03/05/2016	2.0
Information Sheet	Feasibility Study Part 3 Consent Form_v2_3May2016	03/05/2016	2.0
Information Sheet	Acceptability Study Consent Form_v2_3May2016	03/05/2016	2.0
Covering Letter	LSHTM Ethics Response_Morgan_v1.0_4May2016	04/05/2016	1.0
Local Approval	Makerere University_KMC Study Approval 3740001	04/05/2016	1.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerel ,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

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COLLEGE OF HEALTH SCIENCES
SCHOOL OF PUBLIC HEALTH
HIGHER DEGREES, RESEARCH AND ETHICS COMMITTEE

April 18th, 2016

Melissa Morgan, MD MSc
Principal Investigator, Protocol (374)
Post-Doctoral Fellow in Preterm Birth
University of California San Francisco

Re: Approval of a feasibility study protocol (formative Phase) titled: The OMWaNA Study: Feasibility and acceptability of an individually randomized trial of early kangaroo mother care for clinically unstable infants weighing ≤2000g in Uganda

This is to inform you that, the Higher Degrees, Research and Ethics Committee (HDREC) has granted approval to the above referenced study, the HDREC reviewed the above referenced proposal and responses to comments for the related protocol during the 138th meeting held on 12th April, 2016 and has thus granted approval.

Please note that your study protocol number with HDREC is **374**. Please be sure to reference this number in any correspondence with HDREC. Note that the initial approval date for your proposal by HDREC is 18th/04/2016, and therefore approval expires at every annual anniversary of this approval date. The current approval is therefore valid until: **17th/04/2017**.

Continued approval is conditional upon your compliance with the following requirements:

1) No other consent form(s), questionnaire and/or advertisement documents should be used. The consent form(s) must be signed by each subject prior to initiation of any protocol procedures. In addition, each subject must be given a copy of the signed consent form.

2) All protocol amendments and changes to other approved documents must be submitted to HDREC and not be implemented until approved by HDREC except where necessary to eliminate apparent immediate hazards to the study subjects.
3) Significant changes to the study site and significant deviations from the research protocol and all unanticipated problems that may involve risks or affect the safety or welfare of subjects or others, or that may affect the integrity of the research must be promptly reported to HDREC.
4) All deaths, life threatening problems or serious or unexpected adverse events, *whether related to the study or not,* must be reported to HDREC in a timely manner as specified in the National Guidelines for Research Involving Humans as Research Participants.

Makerere University School of Public Health
Higher Degrees, Research and Ethics Committee
Valid Thru:
17 APR 2017

- Please complete and submit reports to HDREC as follows:

a) For renewal of the study approval – complete and return the continuing Review Report – Renewal Request (Form 404A) at least 60 days prior to the expiration of the approval period. The study cannot continue until re-approved by HDREC.

b) Completion, termination, or if not renewing the project – send a final report within 90 days upon completion of the study.

- Finally, the legal requirement in Uganda is that all research activities must be registered with the National Council of Science and Technology. The forms for this registration can be obtained from their website www.uncst.go.ug. Please contact the Administrative Assistant of the Higher Degrees, Research and Ethics Committee at wtusiime@musph.ac.ug or telephone number (256)-393 291 397 if you encounter any problems.

Yours sincerely

[redacted]

Dr. Suzanne Kiwanuka

Chairperson: Higher Degrees, Research and Ethics Committee

Enclosures:

a) A stamped, approved study documents (informed consent documents):

Uganda National Council for Science and Technology

(Established by Act of Parliament of the Republic of Uganda)

Our Ref: HS 2031 16th May 2016

Melissa Morgan
School of Public Health
Makerere University
Kampala

Re: Research Approval: The OMWaNA Study: Feasibility and Acceptability of an Individually Randomized Trial of Early Kangaroo Mother Care for Clinically Unstable Infants weighing ≤2000g in Uganda

I am pleased to inform you that on **02/05/2016**, the Uganda National Council for Science and Technology (UNCST) approved the above referenced research project. The Approval of the research project is for the period **02/05/2016** to **02/05/2017.**

Your research registration number with the UNCST is **HS 2031.** Please, cite this number in all your future correspondences with UNCST in respect of the above research project.

As Principal Investigator of the research project, you are responsible for fulfilling the following requirements of approval:

1. All co-investigators must be kept informed of the status of the research.
2. Changes, amendments, and addenda to the research protocol or the consent form (where applicable) must be submitted to the designated Research Ethics Committee (REC) or Lead Agency for re-review and approval **prior** to the activation of the changes. UNCST must be notified of the approved changes within five working days.
3. For clinical trials, all serious adverse events must be reported promptly to the designated local REC for review with copies to the National Drug Authority.
4. Unexpected events involving risks to research subjects/participants must be reported promptly to the UNCST. New information that becomes available which alters the risk/benefit ratio must be submitted promptly for UNCST review.
5. Only approved study procedures are to be implemented. The UNCST may conduct impromptu audits of all study records.
6. A progress report must be submitted electronically to UNCST within four weeks after every 12 months. Failure to do so may result in termination of the research project.

Below is a list of documents approved with this application:

	Document Title	Language	Version	Version Date
1.	Research proposal	English	3.0	March 2016
2.	Participant Information Sheet and Consent Form	English and Lusoga	3.0	March 2016
3.	Data Collection Tool	English	3.0	March 2016
4.	Recording Sheet	English and Lusoga	3.0	March 2016
5.	Interview Topic guide	English	3.0	March 2016
6.	Semi Structured Interview Guide	English and Lusoga	3.0	March 2016

Yours sincerely,

[redacted]
Hellen. N. Opolot
for: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

cc. Chair, College of Health Sciences School of Public Health, Higher Degrees, Research Ethics Committee

LOCATION/CORRESPONDENCE

Plot 6 Kimera Road, Ntinda
P. O. Box 6884
KAMPALA, UGANDA

COMMUNICATION

TEL: (256) 414 705500
FAX: (256) 414-234579
EMAIL: info@uncst.go.ug
WEBSITE: http://www.uncst.go.ug

A.7. Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa (OMWaNA): protocol for a randomised controlled trial to examine mortality impact in Uganda. Trials 2020.

A.7.1. Copyright and permissions

A.7.2. Web appendix of published paper

Available at: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-4044-6

A.7.3. Ethical approvals

Ethical approval for the study was obtained from the Research Ethics Committees of LSHTM (#16972), MRC/UVRI and LSHTM Uganda Research Unit (GC/127/19/06/717), and UNCST (HS 2645). Letters of approval from LSHTM, MRC/UVRI and LSHTM Uganda Research Unit, and UNCST are available on the following pages.

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Observational / Interventions Research Ethics Committee

Prof Joy Lawn
LSHTM

11 July 2019

Dear Prof Joy Lawn ,

Study Title: The OMWaNA Study: Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa: a multi-site randomised controlled trial to examine mortality impact in Uganda

LSHTM ethics ref: 16972

Thank you for your application for the above research, which has now been considered by the Interventions Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Other	GCP_GCP Certificate (R2)_CT_12Dec17	12/11/2017	n/a
Other	RETC_Certificate_2019	09/01/2019	n/a
Information Sheet	ICFphotography_OMWaNA_V1.0_8.2.19	08/02/2019	1.0
Information Sheet	ICFquali_OMWaNA_V1.0_English_8.02.19	08/02/2019	1.0
Other	Melissa Medvedev_GCP Certificate_5May2019	05/05/2019	n/a
Investigator CV	Cally Tann_CV	30/05/2019	n/a
Investigator CV	Melissa Medvedev_CV	30/05/2019	n/a
Investigator CV	Peter Waiswa_CV	30/05/2019	n/a
Investigator CV	Joy Lawn_CV	30/05/2019	n/a
Investigator CV	Liz Allen_CV	30/05/2019	n/a
Sponsor Letter	2019-MUU-234_Sponsor Confirmation	31/05/2019	n/a
Protocol / Proposal	OMWaNA protocol_V1.2_31.05.19_clean	31/05/2019	1.2
Information Sheet	ICF_OMWaNA_V1.1_English_31.05.19_clean	31/05/2019	1.1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

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Uganda National Health Research Organisation

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Tel: +256 414 320 385 / 6
Fax: +256 414 320 483
Email: directoruvri@uvri.go.ug

REPUBLIC OF UGANDA

Our Ref: GC/127/19/06/717

Your Ref:

UVRI REC APPROVAL NOTICE

To: Dr. Cally Tann, Principal Investigator

Re: Application Tittle: **"The OMWANA study: Operationalizing kangaroo mother care before stabilization among low birth weight Neonates in Africa: a multi-site randomized controlled trial to examine mortality impact in Uganda."**

Type: [✓] Initial Review

I am pleased to inform you that REC meeting 04 convened on May 30, 2019 the UVRI REC voted to approve the above referenced application.

Approval of research is for the period of June 12, 2019 to June 12, 2020.

This research is for considered minimal risk for pediatric risk category. [✓] check box if not applicable

As principal investigator of the research, you are responsible for fulfilling the following requirements of approval:

1. All co-investigators of the research must be kept informed of the status of research.
2. Changes, amendments and addenda to protocol or the consent form must be submitted to the REC for review and approval **prior** to activation of changes. The REC application number assigned to the research should be cited in any correspondence.
3. Reports of unanticipated problems involving risks to participants or other must be submitted to the REC. New information that becomes available which could change the risk: benefit ratio must be submitted to REC.
4. Only approved consent forms are to be used in enrollment of participants. All consent forms signed by subjects and/or witness should be retained on file. The REC may conduct audits of all study records, and consent documentation may be part of such audits.
5. Regulations require review of an approved study not less than once per 12-month period. **Therefore, a continuing review application must be submitted to REC eight weeks** prior to the **above expiration date of** June 12, 2020 **in order to continue with the study beyond the approved period.** Failure to submit a continuing review application in timely fashion may result in suspension of the study. At which point new participants may not be enrolled and currently enrolled participants must be taken off the study.

6. You are required to register the research protocol with the Uganda National Council of Science and Technology (UNCST) for final clearance to undertake the study in Uganda.

NOTE: This study, being considered high risk will be closely monitored by the REC.

The following is the list of all documents approved in this application by UVRI REC:

Document Tittle	**Language**	**Version**	**Date**
OMWaNA protocol	English	1.1	17th May 2019
OMWaNA ICF (English, Luganda and Lusoga)	English, Luganda & Lusoga.	1.0	8th February 2019
OMWaNA ICF Photography and medical images (English, Luganda and Lusoga)	English, Luganda & Lusoga.	1.0	8th February 2019
OMWaNA ICF Qualitative (English, Luganda and Lusoga)	English, Luganda & Lusoga.	1.0	8th February 2019

Yours sincerely,

[redacted]

Dr. Tom Lutalo
Chair, UVRI REC
C.C Secretary, UVRI REC

UGANDA VIRUS RESEARCH INSTITUTE ENTEBBE
RESEARCH ETHICS COMMITTEE
APPROVED
VALID UNTIL
12 JUN 2020
P. O. BOX 49, ENTEBBE
UGANDA

Uganda National Council for Science and Technology
(Established by Act of Parliament of the Republic of Uganda)

Our Ref: HS 2645 **30th August 2019**

Prof. Joy Elizabeth Lawn
Principal Investigator
C/o MRC/UVRI & LSHTM Research Unit
Entebbe

Dear Prof. Lawn,

Re: Research Approval: The OMWaNA Study: Operationalizing Kangaroo Mother Care before Stabilization amongst Low Birth Weight Neonates in Africa: A Multi – Site Randomized Controlled Trial to Examine Mortality Impact in Uganda

I am pleased to inform you that on **20/08/2019**, the Uganda National Council for Science and Technology (UNCST) approved the above referenced research project. The Approval of the research project is for the period of **20/08/2019** to **20/08/2022.**

Your research registration number with the UNCST is **HS 2645.** Please, cite this number in all your future correspondences with UNCST in respect of the above research project.

As Principal Investigator of the research project, you are responsible for fulfilling the following requirements of approval:

1. All co-investigators must be kept informed of the status of the research.
2. Changes, amendments, and addenda to the research protocol or the consent form (where applicable) must be submitted to the designated Research Ethics Committee (REC) or Lead Agency for re-review and approval **prior** to the activation of the changes. UNCST must be notified of the approved changes within five working days.
3. For clinical trials, all serious adverse events must be reported promptly to the designated local IRC for review with copies to the National Drug Authority.
4. Unanticipated problems involving risks to research subjects/participants or other must be reported promptly to the UNCST. New information that becomes available which could change the risk/benefit ratio must be submitted promptly for UNCST notification after review by the REC.
5. Only approved study procedures are to be implemented. The UNCST may conduct impromptu audits of all study records.

LOCATION/CORRESPONDENCE
Plot 6 Kimera Road, Ntinda
P.O.Box 6884
KAMPALA, UGANDA

COMMUNICATION
TEL: (256) 414 705500
FAX: (256) 414-234579
EMAIL: info@uncst.go.ug
WEBSITE: http://www.uncst.go.ug

6. An annual progress report and approval letter of continuation from the REC must be submitted electronically to UNCST. Failure to do so may result in termination of the research project.

Below is a list of documents approved with this application:

	Document Title	Language	Version	Version Date
1.	Research proposal	English	1.1	May 2019
2.	Informed Consent Form (ICF): The OMWaNA study	English, Luganda and Lusoga	1.0	February 2019
3.	ICF: Photography and medical images	English, Luganda and Lusoga	1.0	February 2019

Yours sincerely,

[redacted]

Isaac Makhuwa
For: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

Copied to: Chair, Uganda Virus Research Institute, Research Ethics Committee

A.7.4. SPIRIT Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 5
	2b	All items from the World Health Organization Trial Registration Data Set	2, 3
Protocol version	3	Date and version identifier	35
Funding	4	Sources and types of financial, material, and other support	37
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	37-39
	5b	Name and contact information for the trial sponsor	36
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	36, 37
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	37, 38
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6, 7
	6b	Explanation for choice of comparators	6, 7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10, 11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16-18
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17, 18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	31, 32
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	19, 20
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	22-25
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	26
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	30, 31

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	17, 18
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16, 22
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15,16,22-25
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	20, 21
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	26
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	27
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	27, 28
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	27
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21, 22, 38

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	22
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	36
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	36
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	26
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	37
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	26
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	36
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	36, 37
	31b	Authorship eligibility guidelines and any intended use of professional writers	36, 37
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	36

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	These are available from the correspond-ing author on request.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Biological specimens will not be collected for use in the current trial or in future ancillary studies.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

A.8. Presentations resulting from this work and related work

1. Medvedev M (on behalf of the NMR-2000 team). An example of how the National Neonatal Research Database has been used to help develop a risk scoring tool for use in low- and middle-income countries. *National Neonatal Audit Programme and Neonatal Data Analysis Unit Collaborators' Meeting* 2020 March (postponed due to COVID-19 pandemic); London, UK. Platform presentation.
2. Medvedev M (on behalf of the OMWaNA team). The OMWaNA Trial: Operationalising kangaroo Mother care among unstable low birth Weight Neonates in Africa. *Impact Now: Improving maternal, newborn and child health in Africa* 2019 November; Stellenbosch, South Africa. Platform presentation and panel discussion.
3. Morgan M, Spindler H, Nambuya H, Nalwa GM, Namazzi G, Waiswa P, Otieno P, Cranmer J, Walker D. Clinical cascades to assess facility readiness for neonatal care in Kenya and Uganda. *Pediatric Academic Societies Meeting* 2018 May; Toronto, Canada. Platform presentation.
4. Morgan M, Nambuya H, Waiswa P, Tann C, Elbourne D, Allen E, Lawn J. The OMWaNA Study: Operationalising kangaroo Mother care among unstable low birth Weight Neonates in Africa: a randomised controlled trial to examine impact on mortality in Uganda. *International KMC Congress* 2016 November; Trieste, Italy. Platform presentation.
5. Cooper H, Morgan M, Lawn J. Current practice of kangaroo mother care: facility-based observations and perceptions of home-based care in Uganda. *International KMC Congress* 2016 November; Trieste, Italy. Poster presentation.
6. Morgan M, Nambuya H, Waiswa P, Tann C, Lawn J, Seeley J. Kangaroo Mother Care for unstable infants: acceptability to parents and providers in Uganda. *28th International Congress of Paediatrics* 2016 August; Vancouver, Canada. Poster presentation.
7. Morgan M, Nambuya H, Waiswa P, Tann C, Elbourne D, Allen E, Lawn J. Feasibility of a randomised trial of kangaroo mother care for clinically unstable infants weighing <2000 grams in Uganda. *28th International Congress of Paediatrics* 2016 August; Vancouver, Canada. Poster presentation.

A.9. KMC progress monitoring tool

From: Bergh AM et al. Acta Paediatr 2005; 94: 1102-8

Implementation construct *(and score)*	Progress marker (indicator)	Instrument items related to progress marker *(with scores)*
1 Creating awareness *(maximum = 2 points)*	1-1 Number and type of (senior) managers involved in implementation process (in relation to size of hospital)	• Special persons who take specific effort in promoting KMC – Management (manager, CEO, nursing service manager, ward manager, other) – Professionals (doctors, nurses, allied health workers) – Driving forces (contact person, KMC committee, other individuals or group) *(1.5 points)* • Impressions regarding the intensity of involvement of senior management in establishing KMC (past or future) (a lot, some, little/neutral/resistant) *(0.5 points)*
2 Adopting the concept *(maximum = 2 points)*	2-1 Minuted decision to implement KMC or recall by leaders of occasion and date of decision	• Knowledge of original decision to implement (e.g. occasion, date, minutes, who was involved) • Impression of recall of history of implementation (good, some, none) *(1 point)* • If KMC is not implemented yet: Has a formal decision in this regard been made? *(1 point)*
	2-2 Signing of baseline datasheet to enrol in the outreach	• Baseline data sheet together with permission from the CEO or medical superintendent to participate in the outreach has been submitted *(1 point)*
3 Taking ownership (mobilization of resources) *(maximum = 6 points)*	3-1 Allocation of space	• Practice of intermittent KMC in the neonatal unit (nursery/NICU) *(1 point)* • Special area or ward for continuous KMC 24 h per day *(1 point)*
	3-2 Ability to lodge mothers	• Existence of a lodger mother facility for mothers to stay while infants are still in incubators *(0.5 points)*
	3-3 Procurement of equipment	• Special equipment or facilities enhancing the practice of KMC in the neonatal unit or KMC ward: – Comfortable chairs – Wrappers to hold infant in KMC position – Low beds – Other (e.g. back rests) *(0.5 points)*
	3-4 Removal of cribs	• All cribs removed from KMC ward *(1 point)*
	3-5 Information for mothers	• Availability of brochures and information sheets • Posters on display • Other (e.g. videos) *(1 point)*
	3-6 Other resources	• Allocations from the hospital budget to establish KMC facility *(0.5 points)* • Other sponsors *(0.5 points)*
4 Evidence of practice *(maximum = 7 points)*	4-1 Evidence of the KMC position	• Intermittent KMC practised in high care *(1 point)* • Number of infants doing intermittent KMC in neonatal unit – Observed – Verified from records – Verified other (e.g. from mothers) *(1 point)* • Separate KMC ward or area *(1 point)* • Number of mother–infant pairs enrolled for continuous KMC in separate KMC ward or area in another ward (e.g. postnatal ward) – Number of mothers observed having infants in KMC position *(1 point)*

A.9. KMC progress monitoring tool - continued

From: Bergh AM et al, Acta Paediatr 2005; 94: 1102-8

Implementation construct *(and score)*	Progress marker (indicator)	Instrument items related to progress marker *(with scores)*
	4-2 Orientation for new staff	• Face-to-face oral orientation • Written orientation • Other (e.g. video) *(0.5 points)* (All types of staff orientation to be verified from in-service training or other records)
	4-3 Records that document KMC	• Records in use and nature thereof (ward register, special form for every single KMC infant, special collective record kept for all infants who receive(d) KMC, any other relevant record) *(1 point)*
	4-4 Ability to provide figures of number of infants going through KMC	• Records can be used for calculation of – number of infants receiving intermittent and continuous KMC – length of intermittent and continuous KMC of outreach infant – weight on admission to intermittent and continuous KMC – weight gain while in intermittent and continuous KMC *(1.5 points)*
5 Evidence of routine and integration *(maximum = 7 points)*	5-1 Further evidence of KMC position	• Kangaroo position (skin-to-skin contact) is practised by HIV+ mothers of infants in the neonatal unit and KMC ward *(1 point)*
	5-2 Evidence of KMC nutrition	• There is a *written* feeding policy in the neonatal ward for intermittent KMC and in the KMC ward for continuous KMC *(1 point)*
	5-3 Evidence of KMC discharge and ambulatory KMC (follow-up system)	• Follow-up arrangements (infants return to ward, outpatients, clinic, home care/visits) • Written evidence of follow-up system • Written evidence of record-keeping *(3 points)*
	5-4 Evidence of KMC included in policy and protocol documents	• Statements and policies in which KMC appears (vision, mission, declaration of quality of service) *(0.5 points)* • Guidelines and protocols regarding the practice of KMC (for nursing staff, doctors, ward clerk, allied health workers) *(1.5 points)*
6 Sustainable practice *(maximum = 6 points)*	6-1 Audit results for at least 1 y	• Audit figures containing evidence of ongoing KMC practice for at least 1 y can be provided *(2 points)*
	6-2 Evidence of staff development policy	• Special plan to ensure that all staff get adequate training in KMC *(0.5 points)* • Evidence of a written plan *(0.5 points)* (Also evaluate against the requirements of the South African Skills Development Act)
	6-3 Evidence of staff training (additional to facilitation that is part of the outreach)	• Whether one or more staff members got special training in past year *(1 point)*
	6-4 Score on first five constructs (divided by 12)	(The score on the first five constructs will influence sustainabililty) *(2 points)*
Maximum total score		*30 points*