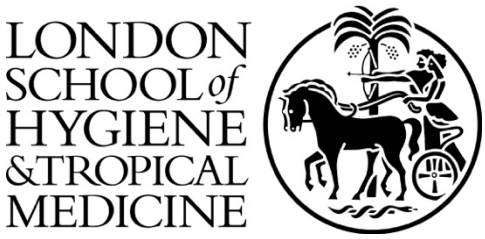

Early Kangaroo mother care for mild-moderately unstable neonates <2000g in The Gambia

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Declaration of own work

I, Helen Brotherton, 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.

Signed: …… Date: ……**7th Feb 2022**……

Abstract

Complications of prematurity are the largest cause of childhood deaths globally, with >1 million deaths and high risk of long-term neurodevelopmental impairment. The first day after birth is the period of greatest risk and greatest potential for improving outcomes, especially with hospital-based small and sick newborn care (SSNC). Kangaroo mother care (KMC) involves continuous skin-to-skin contact and is recommended by WHO for all stable neonates ≤2000g. At PhD onset a priority evidence gap existed for initiation of early KMC before stability, which may contribute towards reducing the Sustainable Development Goal (SDG) for neonatal mortality, especially in low-resource, high-mortality contexts.

My PhD aimed to investigate early KMC (< 24h of admission) in unstable neonates <2000g in one Gambian level 2/2+ neonatal unit. There were four objectives: (1) To prepare the research site with mitigation of barriers to trial implementation; (2) To investigate the effect of early KMC on survival and other clinical outcomes and safety (eKMC trial); (3) To explore pathways to preterm mortality and the effect of early KMC on physiological factors; (4) To determine the programmatic/policy and research implications of the PhD findings.

The first PhD section provides the rationale for studying this topic and description of the local study site context at PhD onset. Substantial site preparations were required for trial implementation, including establishment of KMC as standard care and development/implementation of SSNC guidelines to minimise bias. Local data informed trial protocol development along with a conceptual framework to guide implementation process data collection. Unavailability of the mother during the first 24h of admission was a key recruitment barrier, mitigated by involving female relatives, and informed by a qualitative study to understand their perceptions towards SSNC and KMC.

The second section focuses on the eKMC randomised controlled trial primary and secondary outcome findings. Despite adequate power at trial onset, no evidence of 28-day mortality effect was identified, with possible reasons including (1) Insufficient sample size to detect a between-arm difference due to large reductions in control arm mortality compared to pre-trial mortality (2) Low fidelity of the intervention delivered. However, important insights were gained for secondary outcomes, and feasibility of delivering prolonged KMC contact to unstable neonates, along with safety considerations.

The final section presents a conceptual framework to describe pathways to mortality for neonates <2000g and potential amelioration by early KMC. Exploratory analyses of eKMC trial data identified substantial survival gains during the trial period, with 24% relative mortality reduction for all neonates <2000g and 29% relative risk reduction associated with trial participation. Weight <1200g, hypothermia, hypoxaemia and hyperglycaemia were associated with increased risk of 28-day mortality, with no evidence detected for effect of early KMC on these, or other selected physiological factors.

This PhD provides valuable insights into SSNC in a West African context, underlining the importance of improving quality of SSNC overall as well as the potential for KMC as an entry point for family centred care. Female relatives are key stakeholders for family integrated SSNC and KMC in this socio-cultural context. The eKMC trial findings alone do not support a change to KMC policy, but a recent WHO multi-centre trial is influencing a shift towards immediate KMC. These findings provide rich data and insights into implementation and impact of SSNC, operationalisation of KMC for stable neonates, and novel data regarding the impact, feasibility, and realities of providing early KMC to unstable newborns in a typical African hospital neonatal unit.

Acknowledgements

This PhD spanned 5 years over 2 continents, starting with a political impasse in The Gambia and ending with a family health emergency amidst the COVID-19 pandemic. It has been an incredible personal and professional journey and I was fortunate to work with so many wonderful people along the way.

My stellar team of supervisors at LSHTM and MRC Unit The Gambia (MRCG) have provided unwavering support and intellectual mentorship. Prof. Joy Lawn took a role as my lead supervisor for the Wellcome Trust Fellowship application nearly 7 years ago, and since then she has shaped and supported my academic development through buckets of inspiration, words of wisdom and scientific mentorship. Joy is an incredible advocate for newborn babies and their families, and it has been a privilege to learn from her and be part of her team. Dr Syed Akram Zaman provided supervision in the early stages of the PhD, providing valuable insights to clinical trials and epidemiology as well as a calm approach to navigating MRC Unit The Gambia (MRCG). I am also very grateful to Prof. Simon Cousens for his generous and patient support of my statistical learning over the past 5 years and for face-to-face supervision in 2016. Prof. Anna Roca has been a huge source of inspiration and I highly value her mentorship and have learnt a lot from her extensive clinical trial and epidemiological experience. The other members of my advisory committee were also very supportive, especially Dr Cally Tann who gave valuable clinical and academic inputs and insights into navigating the balance of clinical-academic careers. The Wellcome Trust have been heroic in funding me over the last 5 years, with multiple generous cost extensions in response to the many unforeseen circumstances I encountered along the way, for which I am deeply grateful.

MRC Unit The Gambia at LSHTM is an exceptional research institution, and it was an absolute joy to do my PhD there, as well as to live on the campus as part of the wider community. I give special thanks to Vivat Thomas-Njie for her pearls of wisdom about clinical trials and Karen Forrest for being a good friend and colleague during the COVID-19 pandemic. I am very grateful to the eKMC team of nurses, doctors and field workers, who worked tirelessly and with good humour during the often challenging eKMC trial. The eKMC “family” was a pleasure to lead and the findings of this PhD are a testament to their commitment and hard work. I give huge appreciation to all the staff at EFSTH neonatal and KMC unit, and the Gambian Government Ministry of Health, especially Dr Samateh, Minister of Health, and Dr Bittaye, Director of Health Services, for collaborating so generously and welcoming me into their hospital. Thank you to Mariama Janneh at UNICEF The Gambia, Fatou Camara and Fatty Famara at the former Reproductive Child Health Unit, without which the KMC set up and trial would not have been possible. I would also like to thank friends in The Gambia, London and Edinburgh who have supported and encouraged me throughout this PhD journey, especially the book club ladies, Candlers, de Silvas, Burkes and the Sharmas.

I am deeply grateful to my family (Cian, Roisin and Liam) for all the resilience, love, support and patience they have shown over the past 5 years. Moving continents, schools and jobs is never easy and I appreciate the willingness and joy they showed in embracing change and enjoying our life in The Gambia. I am also very grateful to my late father, from whom I inherited a strong work ethic, and my mother, who always has my back. Finally, I would like to acknowledge all the newborns, mothers and families who took part in this research, without whom it would not have been possible and for whom, ultimately, the work is intended.

COVID-19 impact statement

As for many people across the world, COVID-19 has had a huge direct and indirect impact on my personal and professional life, including the conduct and completion of this PhD during 2020 – 2021.

The COVID-19 pandemic began whilst the eKMC trial was still ongoing and, along with all other research at MRCG, recruitment was paused in March 2020 in-line with Gambian Government national recommendations as per the national lock-down. This was necessary for both safety and well-being of research staff as well as to comply with institutional (MRCG) recommendations for cessation of research and to enable clinical services to prepare for the imminent pandemic in The Gambia. As this was two months prior to the intended trial end date, the eKMC Trial Steering Committee (TSC) decided to stop the trial early. This impacted on achievement of the target sample size and the power of the trial to detect an effect of the intervention, which is discussed in Chapter 8 of this thesis.

To support the MRCG clinical and leadership response to the pandemic I took a paid secondment from my Wellcome Trust fellowship from 1st April to 1st September 2020. I was a member of the three-person "COVID-Clinical leadership" team and contributed towards clinical service re-configuration to establish a 40-bed COVID-19 ward at MRCG and develop guidelines, SOPs, and training materials for COVID-19 clinical care. Along with one other consultant colleague we provided senior medical input at the MRCG COVID ward whilst simultaneously recruiting and training colleagues to join the COVID-19 clinical team. I was invited to sit on the MRCG-COVID leadership panel (April-Sept 2020) and contributed to higher level decisions about pandemic preparation and clinical / laboratory response at MRCG. During this time, I also contributed to the implementation of a COVID-19 community surveillance study (ILI-COVID) and the design of a COVID-19 treatment trial (PaTS trial: Clinicaltrials.gov ref: NCT04703608).

Whilst this was a professionally stimulating time, it required full-time plus commitment and workload which resulted in a 6-month delay to eKMC trial data analysis, publication, and PhD write-up. It was also a very stressful time with the uncertainty of the early pandemic phase and national lockdowns/school closures. The delay to my PhD was compounded by a change in my personal circumstances due to major illness in a close family member. We had to unexpectedly relocate back to the UK in September 2020, from where I completed the analysis and write-up of this thesis alongside caring for my family during the continuing UK COVID-19 restrictions of early-mid 2021.

To off-set the effects of the COVID-19 pandemic on the research and my PhD, I was granted a 6-month extension to my Wellcome Trust Fellowship which included compassionate leave and renumeration for the Clinical COVID-19 secondment. This support mitigated the potential impact of the COVID-19 pandemic on the research in this thesis and enabled me to complete this PhD within timelines.

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Definitions

Adverse event: Any unfavourable and unintended sign, symptom, laboratory finding or disease which is temporally associated with the use of an investigational product[1]

All-cause mortality: Death of a neonate due to any reason within a defined time period

Apgar score: Scoring system for a standardised newborn assessment after delivery, comprising of 5 components: 1) colour; 2) heart rate; 3) reflexes; 4) muscle tone; and 5) respiration. Each component is scored 0 – 2 at 1 minute and 5 minutes post-delivery and at 5-minute intervals up-to 20 minutes for neonates scoring <7[2]

Apnoea: No spontaneous breathing for 1) More than 20 seconds or 2) Less than 20 seconds and associated with one or more of: Colour change; hypoxaemia (SPO_2 <88%) or bradycardia (heart rate <100 bpm)

Duration of admission: Time from hospital admission to discharge (first admission only)

Hyperglycaemia: Blood glucose concentration >6.9 mmol/L, as measured by bedside testing[3]

Hypoglycaemia: Blood glucose concentration <2.6 mmol/L, as measured by bedside testing[3]

Hypothermia: Axillary temperature less than the normal range (36.5^{O}C – 37.5^{O}C) and can be sub-categorised as:[4]

Mild hypothermia/"cold stress":	36.0^{O}C – 36.4^{O}C
Moderate hypothermia:	32.0^{O}C – 35.9^{O}C
Severe hypothermia:	<32.0^{O}C

Hyperthermia: Axillary temperature more than 37.5^{O}C[4]

Low birth weight: Live newborn with birthweight <2500g, can be sub-categorised as:[5]

Very low birth weight:	Birth weight 1000 - 1499g
Extremely low birth weight:	Birth weight <1000g

Kangaroo mother care (KMC): Package of care consisting of prolonged skin to skin contact (SSC) between neonate and caregiver; promotion of exclusive breast milk feeding and early hospital discharge with close follow up:[6]

Continuous KMC:	SSC between neonate and caregiver for at least 18h/day
Intermittent KMC:	SSC between neonate and caregiver periodically of ≥1h duration per session
Early KMC:	Initiation of SSC within 24h of neonatal unit admission

Major congenital malformation: A malformation present at birth and incompatible with life or requires immediate surgical management

Neonatal mortality rate: Number of neonates dying before reaching 28 days of age, per 1000 live births per year[7]

Neonatal period: Period from birth to 28 days, can be sub-categorised as:[8]

Ealy neonatal period:	0 – 6 days after delivery (inclusive)
Late neonatal period:	7 – 28 days after delivery (inclusive)

Preterm birth: Live birth before 37 completed weeks gestation, can be sub-categorised as:[9]

Extremely preterm:	Birth at <28+0 weeks gestation
Very preterm:	Birth at 28+1 – 31+6 week's gestation
Moderate-late preterm:	Birth at 32+0 – 36+6 week's gestation

Severe jaundice: Jaundice occurring within the first 24h after delivery and/or visible in sclera, palms, or soles[3]

Small for gestational age: Birth weight below the 10th percentile for gestational age compared to a gender-specific reference population[5]

Stable: SPO2 ≥88% **in air** for 10 minutes AND all:[10]

- Respiratory rate 20 – 60 breaths/min
- No apnoeic episodes requiring bag-valve-mask ventilation
- No severe chest indrawing

Mildly unstable: A. SPO2 <88% **in air** for >5 minutes AND all:[10]

- Respiratory rate 60 – 100 breaths/min
- No apnoeic episodes requiring bag-valve-mask ventilation
- No severe chest indrawing

OR

B. SPO2 <88% **in oxygen** for >5 minutes AND none of:

- Respiratory rate 60 – 100 breaths/min
- Severe chest in-drawing
- Apnoeic episodes requiring bag-valve-mask ventilation

Moderately Unstable: A. SPO2 ≥88% **in oxygen** for >5 minutes AND 1 of:[10]

- Respiratory rate <20 or >60 breaths/min
- Severe chest in-drawing
- Apnoea requiring bag-valve-mask ventilation
- HR <100 or >200 beats/min

OR

B. SPO2 <88% **in oxygen** for >5 minutes AND none of:

- Respiratory rate <20 or >100 breaths/min
- Severe chest in-drawing

- Apnoea requiring bag-valve-mask ventilation
- Heart rate <100 or >200 beats/min
- bubble CPAP (bCPAP)

Severely unstable: Either:

A. SPO2<88% in oxygen for >5 minutes AND ≥1 of the following:
   - Respiratory rate <20 or > 100 breaths/min
   - Severe chest in-drawing
   - Apnoea needing bag-valve-mask ventilation
   - HR <100 or >200 beats/min

OR

B. bCPAP is required on clinical grounds as per protocol criteria[10]

Suspected late onset infection: New onset of any 1 of the following at >72h of age: Pallor; Lethargy; Jaundice; Apnoea; Hepatomegaly[11] AND negative or unavailable blood or CSF culture

Confirmed late onset infection: New onset of any 1 of the following at >72h of age: Pallor; Lethargy; Jaundice; Apnoea; Hepatomegaly[11] AND blood or CSF culture positive for known pathogen

Serious Adverse Event: Any untoward medical occurrence which:[1]

a) Results in death
b) Is life threatening
c) Requires prolonged hospitalisation
d) Results in persistent or significant disability/incapacity

Abbreviations

AE	Adverse event	**GNB**	Gram-Negative Bacilli
AMR	Antimicrobial resistance	**HAI**	Hospital acquired infection
AOP	Apnoea of prematurity	**HCW**	Health Care Worker
aSCRIP	Adjusted Stability of Cardio-Respiratory in Preterm Infants	**HIC**	High income country
bCPAP	Bubble continuous positive airway pressure	**HIV**	Human Immunodeficiency virus
BP	Blood pressure	**HMIS**	Hospital Management Information Systems
BPD	Bronchopulmonary dysplasia	**HPA**	Hypothalamic-pituitary axis
BSI	Blood stream infection	**HR**	Hazard Ratio
CI	Confidence interval	**HR**	Heart Rate
CFR	Case fatality rate	**ICD**	Informed consent document
CLSI	Clinical and Laboratory Standards Institute	**ICH**	International Conference on Harmonization
CONSORT	Consolidated Standards of Reporting Trials	**IPC**	Infection Prevention Control
Cm	Centimetres	**IQR**	Interquartile Range
CRP	C reactive protein	**IRA**	Intrapartum related asphyxia
CRT	Capillary refill time	**IUGR**	Intra-uterine Growth Restriction
CSF	Cerebral spinal fluid	**IV**	Intravenous
CT	Computed Tomography	**IVH**	Intraventricular Haemorrhage
DSMB	Data Safety Monitoring Committee	**KMC**	Kangaroo Mother Care
eCRF	Electronic case report form	**LBW**	Low Birth Weight
EC	Ethics committee	**LMIC**	Low-middle income country
EFSTH	Edward Francis Small Teaching Hospital	**LSHTM**	London School of Hygiene & Tropical Medicine
ELBW	Extremely Low Birth Weight	**LSM**	Local safety monitor
ENAP	Every Newborn Action Plan	**MD**	Mean difference
FBC	Full Blood Count	**MDG**	Millennium Development Goal
FCC	Family Centred care	**MDR**	Multi-Drug Resistant
FIC	Family integrated care	**MPDSR**	Maternal and Perinatal Death Surveillance and Response Systems
GCP	Good clinical practice	**MRC**	Medical Research Council
GEE	Generalised estimating equation	**MRCG**	MRC Unit The Gambia at LSHTM

GGMoH	Gambian Government Ministry of Health	**MRI**	Magnetic resonance Imagine
MRSA	Methicillin Resistant Staphylococcus Aureus	**RDS**	Respiratory Distress Syndrome
NA	Not Available	**RLS**	Resource Limited Setting
NDI	Neurodevelopmental impairment	**ROC**	Receiver Operating Characteristics
NE	Neonatal Encephalopathy	**ROP**	Retinopathy of prematurity
NEC	Necrotising Enterocolitis	**RR**	Risk ratio
NGO	Non-Governmental Organization	**RR**	Respiratory Rate
NGT	Nasogastric tube	**RSV**	Respiratory Syncytial Virus
NICU	Neonatal Intensive Care Unit	**SAE**	Serious adverse event
NIRS	Near Infrared Spectroscopy	**SCC**	Scientific Coordinating Committee
NMR	Neonatal mortality rate	**SD**	Standard deviation
NNU	Neonatal Unit	**SDG**	Sustainable development goal
OFC	Occipital-frontal circumference	**SGA**	Small for gestational age
OR	Odds Ratio	**SPO2**	Peripheral oxygen saturation
pCO2	Partial arterial pressure of carbon dioxide	**SSA**	Sub Saharan Africa
PCR	Polymerase Chain reaction	**SSNC**	Small and sick newborn care
PI	Principal Investigator	**TSC**	Trial steering committee
PN	Parenteral Nutrition	**U5**	Under 5 childhood
POC	Point of Care test	**UHC**	Universal Health Coverage
PSNS	Parasympathetic Nervous System	**USS**	Ultrasound
PVL	Periventricular leukomalacia	**VLBW**	Very Low Birth Weight
RCT	Randomised Controlled Trial	**WASH**	Water Sanitation and Hygiene
MRSA	Methicillin Resistant Staphylococcus Aureus	**RDS**	Respiratory Distress Syndrome
NA	Not Available	**RLS**	Resource Limited Setting

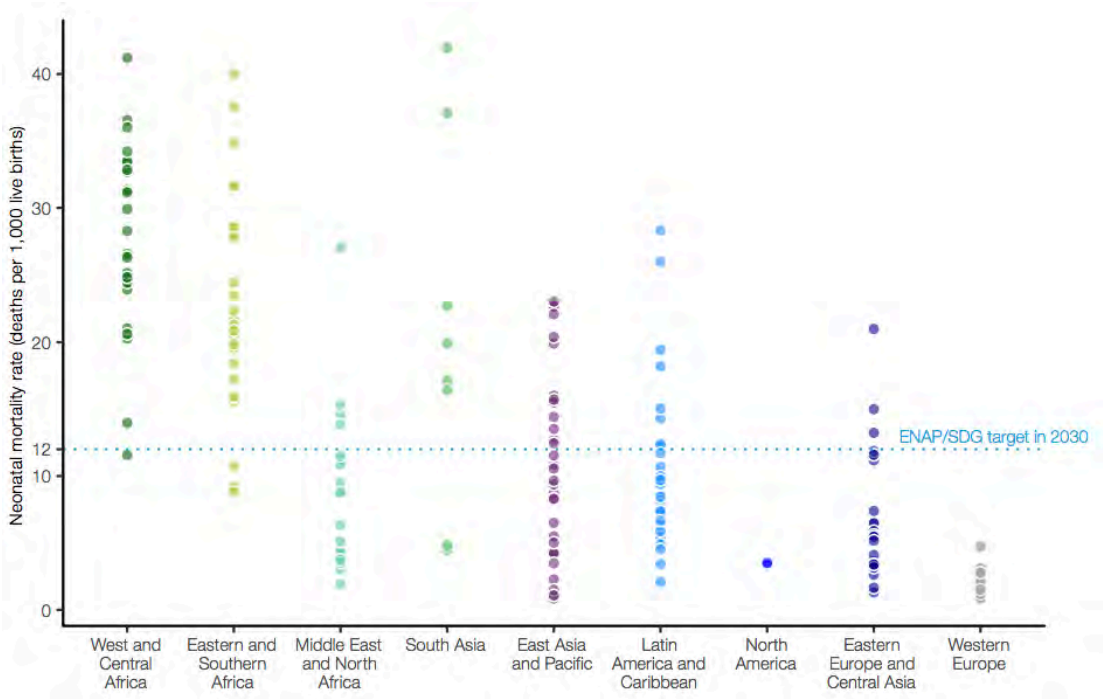
Chapter 1 - Background, rationale and study setting

1.1. Neonatal survival worldwide

1.1.1 Global burden of neonatal mortality

Global neonatal mortality rates (NMR) halved over the last 30 years, from 37/1000 livebirths (1990) to 17/1000 livebirths (2019), reflecting substantial progress in maternal and newborn care during this period (Fig.1-1).[12] However, neonatal mortality still remains unacceptably high with an estimated 2.4 million neonates not surviving in 2019, equating to nearly 5 deaths per minute globally.[12] Nearly all (98%) neonatal deaths occur in low and middle income countries (LMIC), mostly in Asia and Sub-Saharan Africa (SSA), with large inter-and intra-regional variations (Fig.1-1). Sub-Saharan Africa has the highest NMR of all global regions, with 1 million newborn deaths, and the SSA region with the highest NMR is West and Central Africa at 31 deaths/1000 live births.[12]

Figure 1-1. Neonatal mortality rates by global region (2018)



Source: UNIGME report, 2019.[13] Copyright © 2019 by the United Nations Children's Fund. Reproduced with permission.
Abbreviations: ENAP = Every Newborn Action Plan; SDG = sustainable Development Goals

The global NMR is declining at a slower rate than that for children under 5yrs, and neonatal deaths now account for 47% of all under 5 deaths globally.[12] Over the past twenty years the rate of decline has accelerated in many countries but large disparity in progress, both between and within regions exists, especially in SSA (Fig 1-1). There is also large regional variation across the African continent, with the average annual rate of NMR reduction in West-Central Africa only 1.9% compared to 2.5% in Eastern-Southern Africa.[12] The total number of neonatal mortalities did not decline from 1990 – 2019 in nearly half of SSA countries and overall, the number of neonatal deaths in SSA remained stagnant at approximately 1 million.[12] This is attributed to rapid population growth and high birth rates, coupled with a low average annual rate of reduction. This trend risks

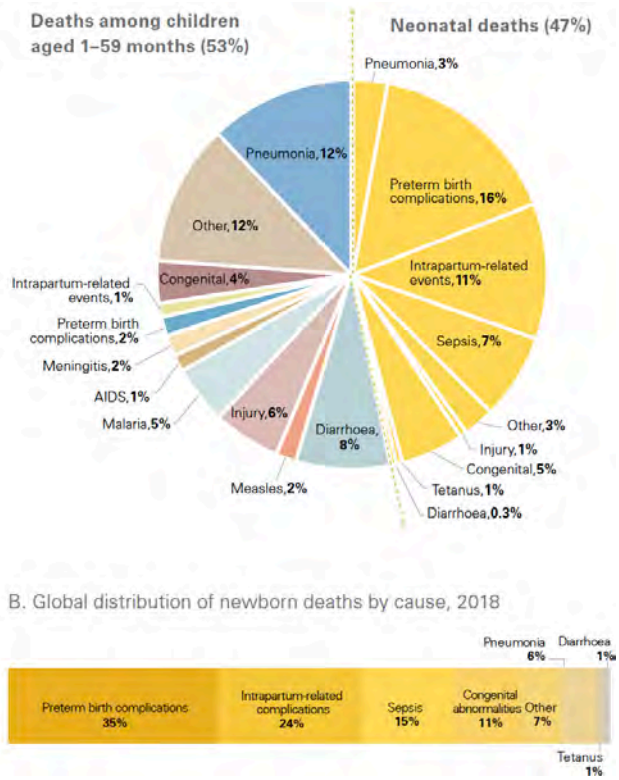
increasing the proportion of neonatal mortalities within the childhood U5 population group in SSA unless the rate of neonatal mortality reduction is rapidly accelerated.

1.1.2 Causes and timing of neonatal mortality

Complications of preterm birth are the single most common direct cause of death for children under-5 (16%) and for neonates (35%), according to the most recent global estimates of death attribution for 2019 (Fig.1-2).[13] Intrapartum related complications, attributed to 24% of neonatal mortalities and infections (combined sepsis pneumonia; diarrhoea; tetanus), accounting for 23%, are other important causes of death.[13] Aetiology of neonatal mortality also varies by postnatal age, with complications of prematurity the dominant cause of death (41%) at <7 days versus sepsis as the main aetiology during the late neonatal period (7-27 days).[14] However, the distinction between complications of prematurity and infections is not clear cut, with prematurity being an important risk factor for acquiring and succumbing to infections yet this is not included in the International Classification of Disease (ICD)10 classification as a complication of prematurity.[15] The specific preterm complications and pathophysiological pathways involved in the pathways to mortality for neonates <2000g will be considered in detail in Chapter 7.

Between one-third [16] and one-half[8] of all neonatal deaths occur on the first day after birth and nearly 75% within the first week.[8, 16] Thus, the early neonatal period, primarily the first 24h after birth is the critical period to focus on improving small and sick newborn care (SSNC) with greatest potential for impact on neonatal survival.

Figure 1-2. Global distribution of deaths among children under age 5 (2018)



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1.1.3 Global action for neonatal mortality: past and present

Newborn mortality came onto the global agenda in the last two-decades, following increased advocacy and awareness of the scale of the issue linked to improved epidemiological estimates.[14, 17] Neonate-specific targets were not included in the Millennium Development Goals (MDG), although were indirectly linked to MDG4, calling for a reduction in under-5 mortality by two-thirds between 1990 – 2015.[18] The marked reductions in child and maternal mortality during the MDG-era highlighted the relatively slower progress in improving neonatal survival and catalysed global focus to improving care and outcomes for vulnerable neonates and stillbirths, especially those born preterm.

Every Newborn Action Plan (ENAP) was endorsed by the World Health Assembly in 2014 and has been instrumental in supporting governments, policy makers and programme managers to implement improvements to newborn care, alongside researching and tracking indicators to measure progress. It is an evidence based roadmap, co-led by WHO and UNICEF, aiming to end preventable newborn deaths with national targets $\leq$12 neonatal deaths per 1000 live births.[19] In 2015 the neonate specific ENAP target was incorporated into the SDG as target 3.2 and neonates were also included in the WHO Global Strategy for Women's, Children's and Adolescent's Health (2016 – 2030) to translate the SDG agenda into a comprehensive "survive, thrive, transform" framework for improving newborn health.[20] Since 2020, there has been increased global recognition of the importance of high quality SSNC in driving down neonatal mortality.[21, 22] Despite the building momentum and shift in global policy, critical implementation gaps still exist for SSNC, of which kangaroo mother care (KMC) is central.

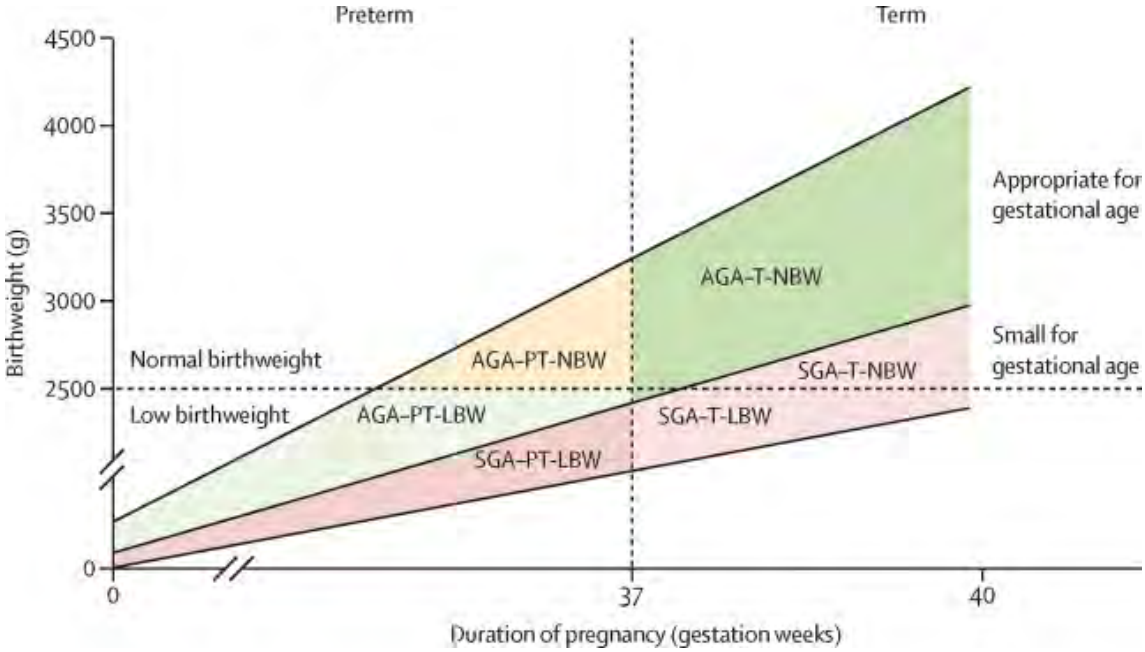
1.2. Small and sick newborns at increased risk

1.2.1 Defining vulnerable newborn phenotypes

Low birthweight (LBW) refers to neonates with birth weight <2500g regardless of gestational age and is further sub-divided into very low birthweight (VLBW; <1500g) and extremely low birthweight (ELBW; <1000g).[23] An estimated 10% of neonates born in SSA are LBW and this group comprise of neonates born preterm, small for gestational age (SGA), or a combination of both, collectively described as "small vulnerable newborn phenotypes"(Fig. 1-3) yet with distinct aetiology and prognosis.[24]

Preterm birth is defined by WHO as being born before 37 completed weeks, or less than 259 days from the date of a woman's last menstrual period.[25] Prematurity is further sub-divided into extremely preterm (<28 weeks), very preterm (28 – 31+6 weeks) and moderate to late preterm (32 – 36+6 weeks). The lower limit of prematurity is difficult to establish and varies between health care contexts, with 22 weeks recommended as the lower limit of viability for resuscitation and management of extremely preterm neonates in some HIC,[26] yet 28 weeks is the lower legal limit of viability in The Gambia.[27] This reflects the likelihood of survival in different health care and socio-cultural-political settings.

Figure 1-3. Definitions of vulnerable newborn phenotypes



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Accurate assessment of gestational age is challenging in settings lacking accurate dating methods, of which the gold standard is first trimester ultrasound. Birth weight <1.5kg is widely accepted as a proxy for prematurity[28] but there is a grey area between 1.5 – 2 kg, which may include moderate-late preterm neonates who are either appropriately grown or growth restricted, as well as term SGA newborns (Fig.1-3). INTERGROWTH-21, an international longitudinal cohort study, reported 2kg as being on the 50th centile birth weight for 33 week gestation neonates.[29]

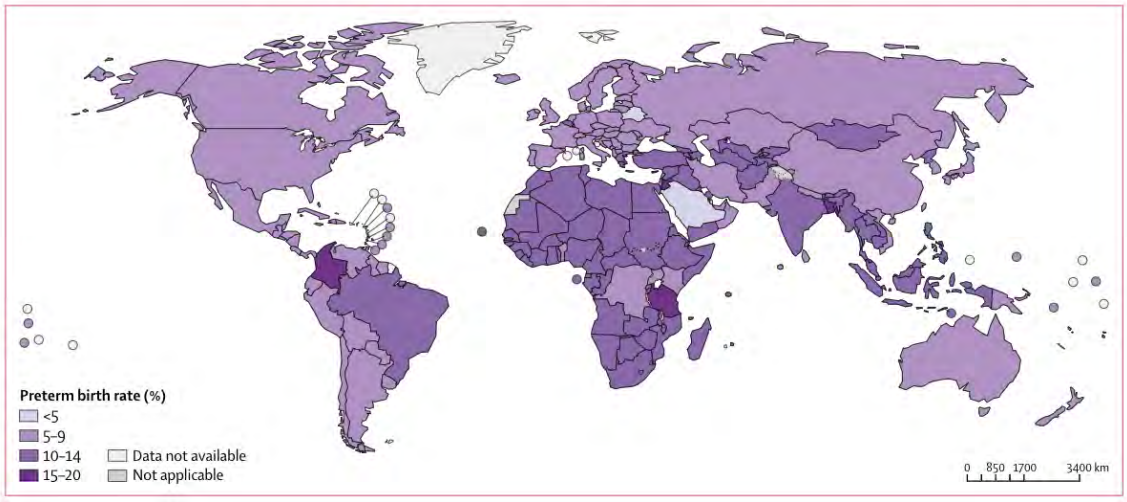
Preterm birth is a complex syndrome encompassing a wide range of overlapping "preterm phenotypes", with 80% linked to specific maternal, fetal or placental conditions.[30] Preterm delivery can be triggered by multiple factors, including maternal illness (e.g., eclampsia, infection), fetal conditions (e.g., genetic syndromes, multiple gestation) or placental complications (e.g., placenta praevia or abruption). In addition, idiopathic preterm delivery may be related to cervical incompetence or occur for no identified reason and elective premature delivery may be required for non-pregnancy related maternal conditions. Hence, preterm neonates should be considered as a heterogeneous group of neonates with distinct clinical and physiological features at different gestational stages with prognosis influenced by prenatal, perinatal, and postnatal exposures.

Growth restriction is variably defined in the literature and the terms "small for gestational age" (SGA) and "intra-uterine growth restriction" (IUGR) are often used interchangeably. In this thesis I will use the term SGA, which was defined by WHO as "birth weight below the 10th percentile for gestational age compared to a gender-specific reference population".[5] An estimated 23 million neonates were born SGA in 2012, with the largest burden in South Asia where 34% of all newborns were estimated to be SGA.[31] Growth restriction can occur for constitutional reasons ("born small") or as a consequence of placental insufficiency, poor maternal nutritional status or other factors such as smoking, as well as linked to fetal aetiology such as multiple births, genetic syndromes or congenital infections.

1.2.2 Burden of global preterm birth

Nearly 15 million babies were born preterm in 2014 according to the most recent global estimates, with 81% of preterm births occurring in Asia and SSA and a trend towards increasing prevalence of global preterm births since 2000.[32] Preterm birth rates vary from 8.7% preterm births/1000 live births in Europe compared to 13.4% in North Africa (Fig.1-4). The majority (80-85%) of preterm neonates are born between 32 to 37 weeks' gestation across all global regions.[32]

Figure 1-4. Estimated global preterm birth rates (2014)



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1.2.3 Contribution of preterm birth to global mortality & morbidity

Being born small is the greatest risk factor for mortality. More than 80% of neonatal deaths in SSA and South Asia occurred in small babies in 2012, of which 65% were attributable to preterm birth.[14] Complications of being born preterm are the direct cause of 1.1 million deaths per year, accounting for an estimated 31% of all neonatal deaths in 2019.[12] The gestational age hugely influences mortality risk with extremely preterm neonates experiencing >95% mortality in the absence of specialised neonatal care[33] and moderate to late preterm neonates experiencing seven-times the risk of mortality compared to term neonates.[34] The highest mortality risk is for neonates who are both preterm and growth restricted[34] and approximately 26% of neonatal deaths are estimated to be attributable to SGA.[31] Different preterm and SGA phenotypes are associated with varying mortality risk, with more severe maternal and placental conditions associated with lower survival.[30] Being born preterm also contributes to reduced survival beyond the newborn period, with preterm, appropriately grown neonates having an estimated 2.2 increased relative risk of post-neonatal mortality and 5.8 increased relative risk for preterm SGA neonates.[34]

Globally, prematurity is the leading cause of neurodevelopmental impairment (NDI) and disability in children, with ≥1 million preterm survivors/year having moderate or severe NDI,[35] mostly those receiving intensive hospital care and increasing risk with decreasing gestational age. SGA is also associated with high risk of mid and longer term morbidity such as stunting[36] and adult onset cardiometabolic disease.[37] Preterm neonates are at least twice as likely as term counterparts to score <10th centile for cognition, fine, gross motor, and language development, with variability in effect size according to the preterm phenotype and gestational age.[33]

1.3. Hospital based small and sick newborn care

Worldwide, ˜30 million neonates require hospital based care every year,[21] often for management of complications of prematurity, and to support thermal control and supplemental feeding until maturity is reached. Over the last decade there has been increased global focus on strengthening existing facility-based systems for provision of timely and high quality hospital care for all newborns but especially those born small and/or sick.[38]

1.3.1 Levels of facility newborn care

Inpatient newborn care is usually delivered across three health-system levels (Fig.1-5): **Primary**, in which basic newborn care ensures warmth, cleanliness and breastfeeding support; **Secondary**, for provision of special care for small and sick newborns, including kangaroo mother care (KMC), gastric tube feeding, intravenous (IV) fluids and oxygen and a transition towards NICU which may include +/- bubble CPAP (bCPAP); and **Tertiary** or neonatal intensive care (NICU) with access to mechanical ventilation, parenteral nutrition, high nurse-newborn ratios and possibly surfactant therapy.[38]

If implemented at scale, small and sick newborn care (SSNC) at secondary, or level 2/2+ neonatal units (NNU) is estimated to avert 70% of neonatal mortality due to complications of preterm birth, with 90% averted with provision of level 3 intensive care.[39] However, many health system bottlenecks for SSNC exist in LMICs, most frequently health financing and health workforce limitations, with leadership/governance, essential equipment and technology and community ownership/partnerships all contributing to reduced scale-up of SSNC.[38]

Figure 1-5. WHO levels of inpatient care of small and sick newborns, with evidence-based interventions

Level	Type of care provided	Standards of care and evidence-based interventions
Primary	**Essential newborn care**	Immediate newborn care (thorough drying, skin-to-skin contact of the newborn with the mother, delayed cord clamping, hygienic cord care); neonatal resuscitation (for those who need it); early initiation and support for exclusive breastfeeding; routine care (Vitamin K, eye care and vaccinations, weighing and clinical examinations); prevention of mother-to-child transmission of HIV; assessment, management and referral of bacterial infections, jaundice and diarrhoea, feeding problems, birth defects and other problems; pre-discharge advice on mother and baby care and follow-up.
Secondary	**Special newborn care**	Thermal care; comfort and pain management; kangaroo mother care; assisted feeding for optimal nutrition (cup feeding and nasogastric feeding); safe administration of oxygen; prevention of apnoea; detection and management of neonatal infection; detection and management of hypoglycaemia, jaundice, anaemia and neonatal encephalopathy; seizure management; safe administration of intravenous fluids; detection and referral management of birth defects. *Transition to intensive care:* continuous positive airway pressure; exchange transfusion; detection and management of necrotizing enterocolitis (NEC); specialized follow-up of infants at high risk (including preterm).
Tertiary	**Intensive newborn care**	Advanced feeding support (e.g. parenteral nutrition); mechanical/assisted ventilation, including intubation; screening and treatment for retinopathy of prematurity; surfactant treatment; investigation and management of birth defects; paediatric surgery; genetic services.

Source: WHO, 2019.[21] Copyright © 2019 WHO. Reproduced with permission

1.3.2 Role of mothers and family members in small and sick newborn care

The capacity of health workers to adequately monitor small and sick neonates on resource-limited NNUs is variable depending on staffing levels, bed occupancy, frequency of admissions and need for emergency management.[40] Mothers and families thus play an important role as caregivers for their

neonates during hospital admission with informal delegation of tasks such as feeding via gastric tube or other supplemental feeding methods, cleaning newborns and changing diapers,[41] and administering oral medications. However, supervision of this informal task-shifting is frequently lacking with education and emotional support for mothers/families considered a low priority in the often over-whelming list of nursing responsibilities.[41]

1.4. Kangaroo mother care as standard care for stable newborns

1.4.1 KMC history, components, and methods of delivery

Kangaroo mother care (KMC) is an evidence-based package of care recommended for all stable, hospitalised babies ≤2000g.[42] It was developed in Colombia in 1978 in response to high neonatal morbidity and mortality, lack of incubators and high rates of infant abandonment.[43] The practice has since been adopted in both HIC and LMIC, yet there is significant heterogeneity in the definition and name, with synonyms including kangaroo method, kangaroo care and skin-to-skin contact. It should be noted that the practice of KMC is distinct from the skin-to-skin contact provided in the first hour after delivery, which is recommended by WHO for all newborns regardless of gestational age and weight, to promote breastfeeding and thermal control.[44]

There are varying definitions of KMC used in the literature and clinical practice, but most include the following three essential components (Fig. 1-6):

1) **Kangaroo position** in which the nearly naked infant is held skin-to-skin against the chest of the KMC provider with baby secured using a wrapper and head held in a slightly extended position to maintain airway patency (Fig. 1-7)
2) **Kangaroo nutrition** which consists of promoting exclusive breastfeeding and supporting feeding using alternative methods (gastric tube, cup, syringe, spoon, paladi) until baby establishes breastfeeding
3) **Kangaroo discharge**, with supportive environment provided by family, health workers and community to enable KMC continuation at home, linked to close health facility follow-up

Figure 1-6. Components of kangaroo mother care

Source: Bergh et al, 2002.[45] Copyright © MRC Unit for Maternal and Infant Health Care Strategies. Reproduced with permission

Although other caregivers can provide skin-to-skin contact, a key aspect of KMC is the stimulation of

maternal breast milk production and subsequent effects on promoting breastfeeding and growth. Hence, the mother is the preferred KMC provider, but substitute providers such as aunties, grandmothers and fathers may be required if mother is not available or is unwell. KMC is an important practice within the family-centred care model based on a collaborative partnership between family and health workers in delivering newborn care.[46] In addition to health worker supervision and support, "social peer networks" with other KMC providers are also encouraged.[47]

Figure 1-7. Gambian preterm neonate in kangaroo position with mother

Source: Louis Leeson/LSHTM, 2019. Reproduced with permission

Newborns should be in the KMC position for as long as possible[42] with previous WHO guidelines recommending 18h/day[6] and the most recent Cochrane systematic review and meta-analysis reporting mortality effect only from studies delivering ≥20h/day in KMC position.[48] Intermittent KMC is provided if the mother is not available or willing to do continuous KMC, if the environment is not conducive or if there is a clinical reason precluding prolonged KMC duration. However, the KMC evidence base does not precisely define what constitutes intermittent versus continuous, with varying definitions in clinical use and the literature. A definition proposed by international KMC experts is "KMC for short periods once or a few times per day, for a variable number of days" and suggests that the two modalities should be regarded as a being on a continuum with the aim of delivering as much time in KMC position as possible.[49]

Weekly or biweekly follow-up at "KMC clinics" after discharge is recommended to identify intercurrent illness, ensure adequate feeding/growth and continue to promote KMC practice in the community. Such an approach enables neonates to be discharged at relatively lower weight compared to conventional care but requires a home-care programme with maternal/family education and community support for KMC. KMC is recommended to continue until the neonate either reaches 2500g or doesn't tolerate being in KMC position, after which time the infant is cared for as per usual practices. Community initiated KMC without facility admission is a related yet separate intervention and is not considered in this thesis.

Although KMC requires no specialist technology or equipment apart from a wrapper to secure the newborn, it meets the definition of being a complex intervention since it "requires

maternal/caregiver compliance with multiple interacting components", [50] with engagement/support from HCW and families being a critical component.[51]

1.4.2 Kangaroo mother care in stable newborns: Evidence for clinical benefit and safety

Several systematic reviews and meta-analyses have synthesised the evidence for clinical effect of KMC, with the most recent Cochrane review (2016) reporting a significant mortality reduction by 40% at discharge or 40-41 weeks postmenstrual age (RR 0.60, CI 0.39-0.92; 8 trials, 1736 infants) and 33% at latest follow-up (RR 0.67, CI 0.48-0.85) compared to conventional incubator care for LBW neonates. Sub-group analysis in the Cochrane 2016 review showed a mortality effect only for the sub-group of trials providing continuous KMC for ≥20h/d, KMC started within 10 postnatal days, studies from LMIC and unstable newborns,[48] although the latter was based on one small study classed as high risk for performance, detection and reporting bias.[52] A mortality effect was not observed in studies conducted in HIC, those using intermittent KMC (defined as <2h/day and 6-15h/day) or studies involving stable newborns. The Cochrane 2016 authors concluded that there was sufficient evidence to support the use of KMC in stabilised LBW infants in resource-limited settings and that the potential benefits on morbidity and mortality would be expected to be greatest in settings in which conventional neonatal care was unavailable.[48] A systematic review and meta-analysis conducted by Boundy et al included both randomised controlled trials and observational studies and reported a slightly lower mortality effect of 36% at latest follow-up for neonates <2000g (RR 0.64, 95% CI 0.46 – 0.89; 15 trials).[53]

Other short-term clinical benefits of KMC include reduced risk of: hypothermia; nosocomial infection/sepsis; severe infection/sepsis with moderate evidence of increased weight,[54] length and head circumference gain and improved exclusive breast feeding at discharge, term and latest follow-up.[48] Improved cardio-respiratory stability and reduced risk of hypoglycaemia have also been reported.[53] Additional benefits for newborns include an analgesic effect when in KMC position for painful procedures,[48, 55] enhanced maternal-infant bonding[53] and reduced stress.[56] Maternal benefits include improved mental health status,[56] increased satisfaction with infant care and involvement of father in home care.[48] KMC is also associated with reduced duration of hospitalisation,[48].which benefits neonates, mothers and families and the health care system. Mid-term benefits on growth, especially head circumference growth index, have been observed but there is less available evidence for the long-term benefits of KMC with limited data from South America for positive neuro-developmental, behavioural, and social benefits at 20-years after KMC delivery[57] and a dearth of data from SSA and Asia.

1.4.3 Need for acceleration of kangaroo mother care scale-up

Despite moderate quality evidence of mortality and clinical benefit, widespread scale-up of KMC for stable newborns has not yet been achieved. Some countries (e.g., Malawi) have successfully scaled-up KMC to all central and district hospitals for the past 15-20 years,[58] and others are yet to implement or have only limited coverage. Within West and Central Africa there is large variation in coverage, ranging from good progress at tertiary and regional hospitals in Ghana,[59] to limited coverage and no national KMC policy in The Gambia. Nearly half (44%) of the Countdown to 2015 countries reported national policies recommending KMC[18] but KMC services are frequently limited to tertiary or teaching hospitals with limited comprehensive service provision.

From 1998 there have been global efforts to accelerate global KMC scale-up, especially since 2013 due to publication of the 'Born too Soon' report[60] and ENAP KMC coverage targets.[19] Other initiatives included establishment of the 'International Network of KMC', which has promoted KMC education and advocacy since 1998,[49] the 'Istanbul Declaration on KMC Acceleration' in 2013,[61] and the subsequent KMC Acceleration Partnership (KAP), which was convened by the Saving Newborn Lives Programme and involved 70 stakeholders committed to accelerating KMC implementation. The KAP set an ambitious target of 50% coverage of KMC amongst preterm neonates by 2020 and emphasised the importance of robust metrics to measure progress in scale-up.[61]

An African/Asian multi-country analysis of health-system barriers to KMC implementation identified that community ownership and health financing factors were important bottlenecks in both high and low-NMR countries. Other important barriers included lack of leadership and governance at national level with absence of national KMC policy or strategy as well as data gaps for understanding KMC coverage.[62] KMC champions at all health systems levels, from front-line health workers to national policy makers, are important enablers for KMC scale-up, with adequate resources for KMC provision being foundational.[62]

1.5. Early kangaroo mother care prior to stability

1.5.1 Rationale for investigating early kangaroo mother care in unstable neonates <2000g

Neonates undergo a physiological transition from in-utero to ex-utero life which includes inflation and aeration of the lungs, haemodynamic shift from placental to systemic circulation and exposure to the external environment with impact on skin, intestinal and neurological systems. This stabilisation typically occurs over the first 6-hours after delivery but can take up-to 24h or beyond to complete, especially if complicated by hypothermia, surfactant deficiency or other complications of prematurity or delivery. This process contributes towards the high mortality risk during the first 24h after delivery[8] and represents a window of opportunity to improve the physiological and clinical trajectory for neonates <2000g. Despite over 40 years of KMC research, there is an evidence gap for using KMC during the early period after delivery for neonates who are not yet fully stable, which was highlighted as a research priority by the Cochrane 2016 review[48] and the most recent WHO preterm care recommendations.[42]

Neonates <2000g represent a predominantly preterm population, including moderate-late preterm infants who are also growth restricted (section 1.2.1). Hence, this weight cut-off was chosen to minimise inclusion of term, growth restricted neonates and is balanced against the risk of excluding appropriately grown late preterm neonates. Neonates with weight equal to 2000g were not included, despite KMC being recommended for neonates $\leq$2000g, to avoid skewing the population more towards term, growth restricted neonates and to avoid data heaping.

1.5.2 Other trials of early kangaroo mother care prior to stability

At the time of PhD onset there were no published clinical trials of early KMC in unstable neonates with adequate power to examine mortality effect (Table 1-1). Worku et al reported 40% reduction in mortality with early KMC in 123 Ethiopian neonates (22.5% vs 38%; p<0.05; RR0.59, 95% CI 0.34 – 1.03) but was underpowered with exclusion of >50% of eligible subjects, had poorly defined case

definitions and selective reporting of outcomes.[52] In a RCT conducted in Madagascar, Nagai et al found no difference in mortality with KMC started at <24h postnatal age compared to standard care in stable neonates but this trial was also underpowered with small sample size (n=73) and low event rates in both arms.[63]

The iKMC trial recently reported a beneficial mortality effect of immediate KMC (~1 hr after delivery) compared to standard care,[64] but this trial had not started at time of PhD onset and will be discussed in detail in Chapter 8. The OMWaNA trial commenced recruitment in 2019 and is currently ongoing at four Ugandan sites and has purposefully similar protocol design to eKMC trial.[65] The risks of bias have been assessed for each trial, as per Cochrane classifications and considering the trial protocols. There is low risk of screening bias for all trials but varying degrees of performance and detection bias due to the nature of the non-blinded intervention and varying mitigation through use of independent outcome assessors in only the iKMC trial[64] and rigorous methods to ensure equivalent care is provided to both arms in the eKMC trial, as will be discussed later in the thesis (Table 1-1).

Table 1-1. Comparison of trials studying mortality effect of early KMC in unstable neonates

	Worku et al[52]	**Nagai et al[63]**	**iKMC[64]**	**eKMC[10]**	**OMWaNA[65]**
Study period	2001 - 2002	2007 - 2008	2017 – 2020	2018 - 2020	2019 - 2022
Country/ies	Ethiopia	Madagascar	India, Malawi, Ghana, Nigeria, Tanzania	The Gambia	Uganda
National Neonatal Mortality Rate at trial onset	48.5	25.8	India (22.7); Malawi (22.4); Ghana (23.9) Nigeria (36); Tanzania (21.3)	26.3	19.9
Trial sites	1 University hospital	1 University hospital	5 national referral hospitals	1 national referral hospital	3 regional referral hospitals & 1 district hospital
Level of newborn care	Special care (level 2)	Special care (level 2)	Intensive care (level 3)	Special care (level 2+ bCPAP)	Special care (level 2+ bCPAP)
Trial design	Individual, superiority, 2-arm	Individual, superiority, 2-arm	Individual, superiority, 2-arm	Individual, superiority, 2-arm	Individual, superiority, 2-arm
Sample size	123	73	3211	279	Target 2188
Inclusion criteria	Singleton; <2000g Mother healthy & willing to participate	<2500g; <24h of age	Singleton or twin; 1 – 1799g; Age 0 – 2h; Mother able to provide KMC	Singleton or twin; <2000g; Age 1 – 24h; KMC provider able & willing; Study bed available	Singleton or twin; 700 – 2000g; Age 1 - 48h; KMC provider able & willing
Exclusion criteria	Major congenital malformation; twin	Prolonged apnoea; Intravenous infusion	Triplets; mother aged <15y; resident outside trial area; unable to breathe on own by age 1h; congenital malformation	Triplets; congenital malformation; seizures; severe jaundice; stable; severe instability; mother/baby in other study	≥Triplets; life-threatening instability; severe jaundice; seizures
Stability definition for target population	Unstable: On oxygen & IV fluids	Relatively stable: SpO2 ≥95%;[a] HR >100bpm; RR <60 bpm; CRT <3 secs	None provided	Mild-moderately unstable[b]	Receiving ≥1 of: Oxygen; bCPAP; IV fluids; antibiotics; phenobarbital
Intervention arm	Continuous KMC to discharge	Continuous KMC to discharge	Continuous KMC until discharge	Continuous KMC until discharge	Continuous KMC until discharge

	(started at 10h, duration not reported)	(started at 19h,[c] duration not reported)	(started at 1.3h, duration 16.9h/d)[c]	(started at 15.2h, duration 6.7h/d)[c]	
Control arm	Cot in heated room	Incubator or radiant warmer KMC at >24h of age	Standard care until stable then continuous KMC	Incubator or radiant warmer until stable then intermittent or continuous KMC at >24h	Incubator/radiant warmer until stable, then intermittent KMC
Primary outcome	In-hospital mortality	Mortality at 28 days	Mortality within 28 days (72h)	Mortality within 28 days	Mortality within 7 days of birth
Result	KMC: 14/62 (23) SC: 24/63 (38) RR 0.57 (95% CI 0.33 – 1)	KMC: 2/37 (5) SC: 1/36 (3) RR 1.95 (95% CI 0.18 - 20.53)	KMC: 191/1596(12) SC: 249/1587 (16) RR 0.75 (95% CI 0.64 – 0.89)	KMC: 29/138 (21) SC: 34/139 (24) RR 0.84 (95% CI 0.55 – 1.29)	NA
Risk of bias:[d]					
Selection	Low/unclear	Low	Low	Low	Low
Performance [e]	High	High	High	Moderate	High
Detection[f]	Moderate	Low	Low	Moderate	Moderate
Attrition[g]	Unclear	Low	Low	Low	NA
Reporting[h]	High	Low	Low	Low	NA

(a) Stability definition does not indicate if oxygen was provided; (b) Stability definition in eKMC trial as per protocol; [10] (c) Median values reported; (d) Risk of bias determined as per Cochrane review classifications for trials included in the meta-analysis.[48] Risk for other trials determined based on review of protocol;[10, 64, 65] (e) High risk of performance bias if no blinding of participants and personnel, allocation arms managed in different environments or if inadequate mitigation of risks; (f) High risk of detection bias assigned if no blinding of outcome assessments, moderate risk assigned if outcome objective and unlikely to be affected by non-blinding, low risk if blinded outcome assessments; (g) High risk of attrition bias if incomplete outcome data (no reporting of lost to follow up & withdrawals); (h) High risk of reporting bias if selective reporting of outcomes. Abbreviations: bCPAP (bubble Continuous Positive Airway Pressure); CRT (capillary refill time); HR (heart rate); IV (intravenous); KMC (kangaroo mother care); NA (Not available); RR (Respiratory rate); SPO_2 (peripheral oxygen saturation)

1.5.3 Measurement challenges affecting kangaroo mother care trials

There are challenges in synthesising outcomes from previous KMC trials due to differences in trial populations and delivery of a varyingly defined intervention. In addition, there are inherent limitations in measuring the KMC "dose" delivered, including lack of evidence to support choice of measurement method.

The underlying vulnerable newborn phenotype, such as SGA, preterm or LBW, influences outcomes[24] and such phenotypes are not consistently measured or reported in KMC trials (Table 1-1) with assessment of SGA phenotypes particularly important. Likewise, the terms "relatively stable or unstable" as mentioned in the Cochrane 2016 review can encompass a wide range of stability levels which are also dependent on the level of supportive treatment required. For example, a neonate may be classed as unstable without any oxygen or supportive care and then stabilise with appropriate respiratory support and could then be termed as unstable or stable, depending on subjective interpretation. Compared to mortality risk scores for use in HIC NICUs, for which there are many validated systems (e.g., CRIB-II, SNAP-II, TRIPS-II), there is a dearth of high-quality, validated risk scores to predict mortality in resource-limited facilities which do not rely on ventilator settings or blood gas values.[66] This makes comparison between KMC trials challenging due to varying populations within different contexts of care (Table 1-1). NMR-2000 is a recently developed, simplified score to predict inpatient mortality for newborns ≤2000g and includes three variables:

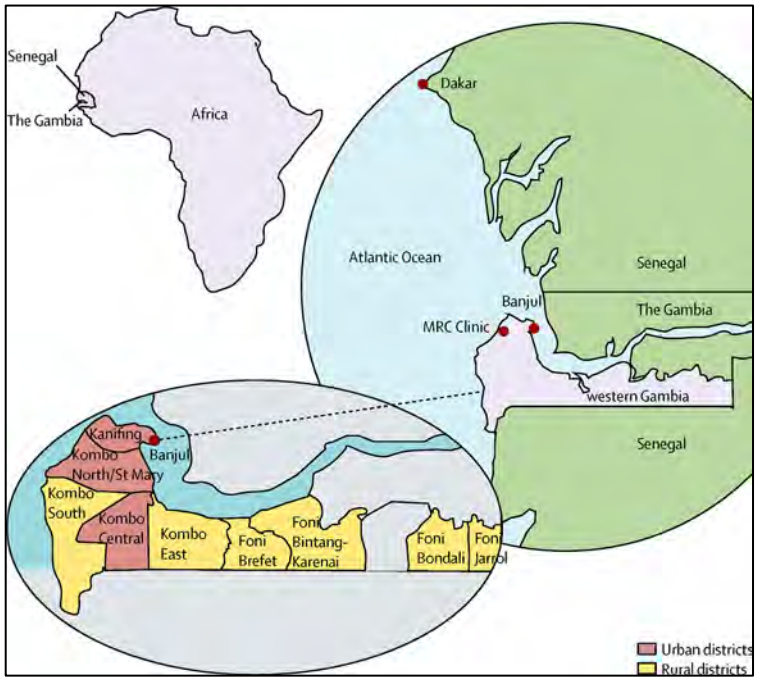
birthweight, admission SpO_2, and highest level of respiratory support (nasal cannula/headbox or bCPAP/invasive ventilation) and has very good discriminatory ability on external validation in UK and Gambian populations (c-index 0.89 in UK sample, 0.82 in Gambian validation sample).[66]

The definition of KMC and adherence to the intervention in previous KMC trials is also highly variable, ranging from skin-to-skin contact for 1h/day to >20h/day with large variation in timing of onset, duration of days KMC provided for and duration of each individual KMC session typically not reported. Similarly, the quality of KMC is not yet defined and lacks international consensus,[67] limiting assessment of differences in quality of the intervention delivery between studies. As well as resulting in different interventions, this also reflects challenges in accurate measurement of precise skin-to-skin contact and limited evidence for validity of measurement methods, such as HCW observation versus KMC provider observation.

1.6. Study setting at PhD onset

This PhD was conducted at the neonatal unit of Edward Francis Small Teaching Hospital (EFSTH), the main neonatal referral unit and only teaching hospital in The Gambia, West Africa. EFSTH is sited in Banjul, the administrative capital within the Western Region (Fig.1-8). Administrative, technical, logistical and laboratory support was provided by MRC Unit The Gambia at LSHTM (MRCG) at the Fajara campus situated 15km from EFSTH (Fig.1-8).

Figure 1-8. Map of The Gambia, West Africa, showing PhD study site in Banjul



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1.6.1 The Gambian context for newborn care

The Gambia is a low-income country in West Africa, ranked 173 out of 187 on the Human Development Index (2015).[68] It is situated on the horn of West Africa, surrounded on three sides by Senegal and adjacent to the Atlantic Ocean (Fig.1-8). The population in 2015 was approximately 2 million, with 3% annual population growth and a high population density.[69] The gross domestic product was 1.38

billion US dollars (2015)[69] with 13% of domestic general government resources used for health expenditure in 2013.[13, 70] The Universal Health Coverage (UHC) service coverage index was 45.0 (2015), indicating that urgent progress is needed to meet SDG 3.8 target of achieving UHC coverage and access to quality essential health-care for all Gambians by 2030.

The NMR in The Gambia was 30 deaths/1000 livebirths in 2015, just less than the regional average for West and Central Africa (31/1000 livebirths) and reducing by 2.2% annually (1990 – 2015).[70] An estimated 14% of all Gambian neonates were born preterm and 10% born LBW in 2015, with complications of prematurity accounting for 28% and 13% of all neonatal and under-5 mortality respectively (Table 1-2). 70] Antenatal coverage was high with 72% of women receiving ≥4 visits, indicating good access and use of primary health services, yet just over half (57%) of women delivered their newborns in a health facility or with a skilled birth attendant during 2009 - 2013 (Table 1-2).[70]

Seasonal variation in prematurity, LBW and SGA birth rates in The Gambia and elsewhere in West Africa is well described. Rates of both SGA and prematurity are lower during the dry season (December – June) compared to the rainy season (July – November), with peaks of SGA births in November and two annual peaks for premature birth in July and October.[71] However, this evidence of seasonal variation was collected from a rural population from 1978 – 2003, when malaria was endemic in The Gambia. It may not reflect recent trends in births of vulnerable phenotypes as there has been a substantial reduction in malaria incidence over the past two decades[72] and observational data indicating that declining malaria burden is reducing LBW prevalence in SSA.[73] In addition, increasing urbanisation and climate change may shift the seasonal trends in premature delivery as pregnant women face different environmental challenges in urban versus rural areas.

Table 1-2. Maternal, newborn and health system indicators for The Gambia, 2015 – 2019

	2015[70]	**2019[12]**
Total population	**1.99 million**	**2.3 million**
Mothers		
Total live births	83,100	88,000
Number of maternal deaths	590	520[a]
Maternal mortality ratio per 100,000 live births	706	597[a]
Newborn		
Number of neonatal deaths	2470	2,300
Neonatal mortality rate per 1000 live births	30	26.3
Average annual rate of NMR reduction (from 2000)	2.2%	2.3%
Proportion of under-5 deaths that are newborn	43%	46%
Low birth weight rate	10%[b]	17%[c]
Number of preterm births	11,600	9,739[c]
Preterm birth rate	14%[d]	12%[e]
Preterm complications as cause of all NMR	28%[f]	26%[a]
Preterm complications as cause of all U5 deaths	13%[f]	13%[a]
Intrapartum related events as cause of all NMR	30%	29%[a]
Sepsis/tetanus as cause of all NMR	21%[f]	21%[a]
Number of still births (2015)	2020	2,020

Stillbirth rate per 1000 total births (2015)	23.9	23.9
Postnatal practices		
Not weighed at birth	21%	21%[g]
Early initiation of breastfeeding (2010-2018)	52%[b]	52%[g]
Exclusive breastfeeding <6 months	34%[h]	47%[i]
Health system	**2015**	**2019**
Antenatal care coverage (≥1 visit)	98%[b]	86%[i]
Antenatal care coverage (≥4 visits)	72%[b]	78%
Skilled attendant at birth	57%[b]	57%
Birth in health facility	56%[b]	63%
Caesarean-section delivery	3%[b]	2%[i]
Physician density per 10,000 population (2015)	1.1	1.1
Nursing & midwifery density per 10,000 population (2015)	16.3	16.3

Data collected in a) 2017; b) 2009 – 2013; c) 2018; d) 2010; e) 2014; f) 2013; g) 2010 – 2018; h)2005 – 2010; i) 2013 – 2018
Abbreviations: NMR = Neonatal mortality rate; U5 = Under 5 years

1.6.2 Small and sick newborn care at the study site

1.6.2.1 Overview of hospital & maternity services

At PhD onset, EFSTH was the only teaching and referral hospital in The Gambia, closely linked to the University of The Gambia. It provided tertiary-level services including general surgery/orthopaedics and intensive care, as well as offering primary health care service to the local Banjul community. Neurosurgery, cardiac and complicated airway surgery (e.g., repair of oesophageal atresia) were not available at EFSTH and neonates were referred to Dakar, Senegal, for specialist paediatric surgery. Hospital facilities included a pharmacy, radiology and physiotherapy departments as well as a range of laboratory services including: blood transfusion (blood grouping; fresh frozen plasma available); microbiology; haematology and biochemistry. EFSTH was a public-sector facility, providing free health care albeit with the option of admission to a small private wing.

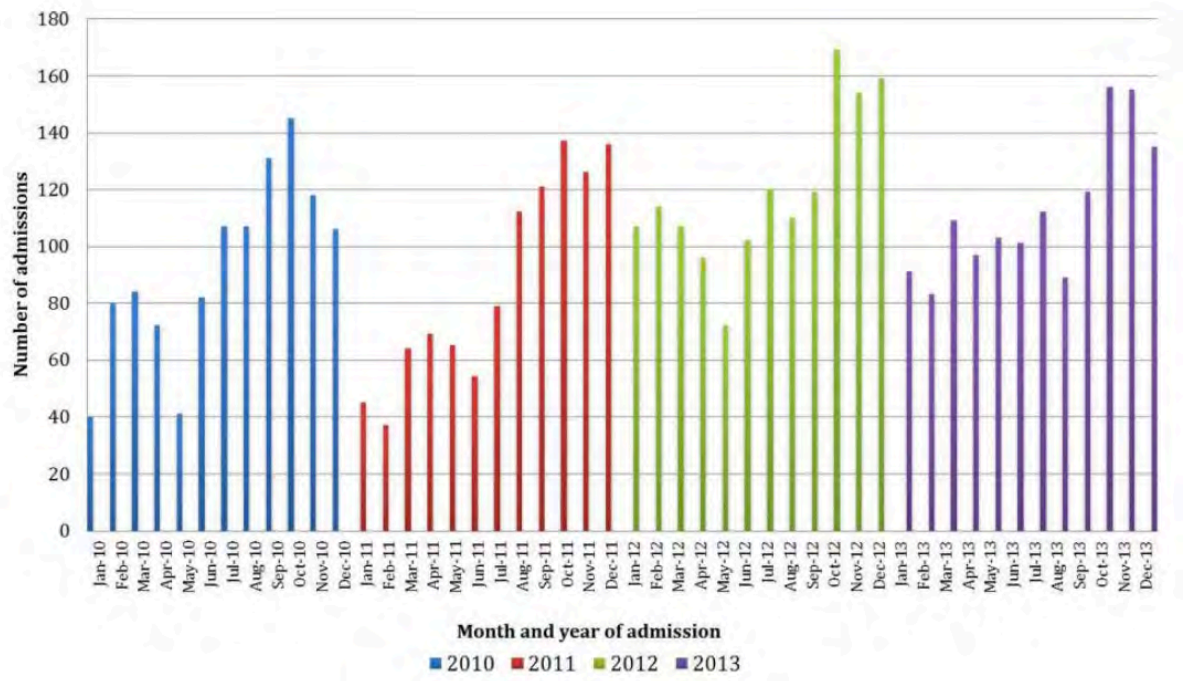
The EFSTH maternity unit delivered approximately 5,000 newborns/year in 2014 with a range of gynaecological and obstetric services including ultrasound, antenatal corticosteroids, and magnesium sulphate. Caesarean-section rates at EFSTH have increased since 2006 with Caesarean-sections comprising 24% of all deliveries in 2014, of which 87% were emergency procedures.[74] Resuscitation of newborns was typically performed by midwives or obstetric medical officers. Stable, term neonates were managed on the maternity postnatal wards, with routine referral to the neonatal unit (NNU) for neonates <1.8kg, those requiring resuscitation at delivery and any other neonate requiring specialist paediatric input. The hospital had not been accredited with UNICEF baby-friendly status at the time of PhD onset.

1.6.2.2 Neonatal unit admissions & in-patient case-fatality rates

Approximately 1400 neonate/year were admitted to the EFSTH neonatal unit (NNU) from 1st January 2010 to 31st December 2013, with seasonal variation including a peak in admissions during the late rainy season (September – November) and quieter periods from January to June (Fig.1-9).[27] Neonates are admitted from several sources across The Gambia, with EFSTH NNU acting as the primary health facility for neonates in the Banjul community as well as the national neonatal referral unit for specialist newborn care, including surgery. One-third of neonatal admissions were born at

the EFSTH maternity unit (in-born), and two-thirds born at other government or private-sector health facilities with approximately 9% of admissions following a homebirth, between 2010 and 2014. Referral pathways were typically via other health facilities, although self-referrals were possible via presentation to the EFSTH Paediatric Outpatient Department and onward triage. Just under half of all neonates were admitted on their first day after delivery (45%) with 55% admitted between day 2 and day 28 postnatal days, predominantly within the first week after delivery (76%)(2010 – 2014).[27]

Figure 1-9. Seasonal pattern of admissions to EFSTH neonatal unit (2010 – 2014)



Source: Okomo et al, 2015.[27] Copyright ©2015, Taylor & Francis. Reproduced with permission

From 1st January 2010 to 31st December 2013, over one quarter (26%) of neonates admitted to EFSTH NNU were premature and one third weighed <2000g. The inpatient neonatal case fatality rate (CFR) increased from 33% (2010) to 39% (2013) during this period with lower admission weight (<1.5kg) associated with higher inpatient mortality risk and 48% CFR for neonates <2000g. Over one-third (39%) of inpatient deaths were attributed to complications of premature birth during the period 2010 – 2014.[27]

1.6.2.3 Newborn care service readiness and systems

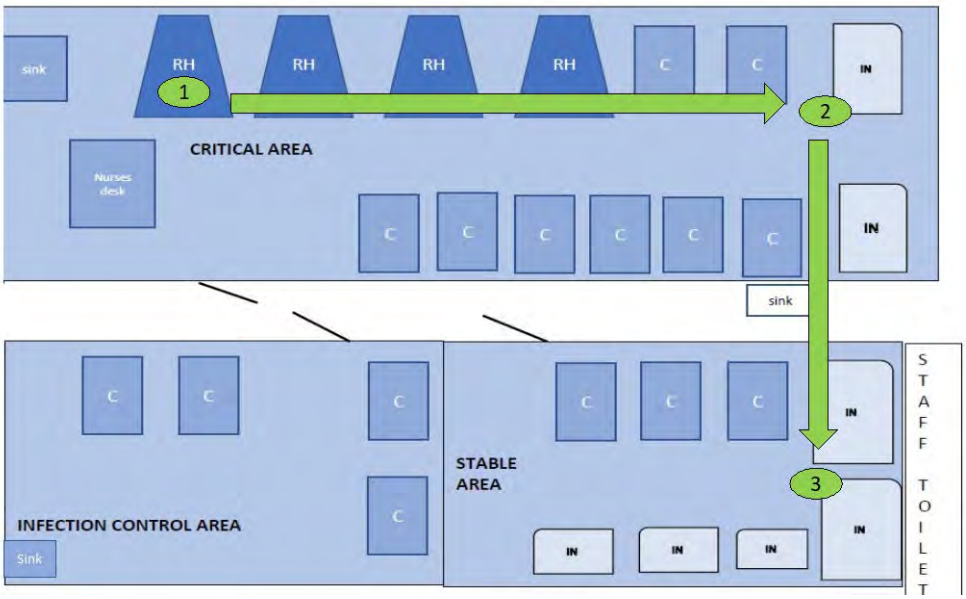
A site survey was conducted at EFSTH NNU from 29th August 2016 to 7th September 2016 as part of this PhD using the Stages of Change Facility Assessment tool[75] and the WHO essential list of requirements for KMC implementation.[45] The aim of this survey was to understand the context of newborn care and existing KMC provision in-order to identify priority actions to prepare the site for the planned clinical trial. A summary of the findings is presented below.

1.6.2.3.1 Patient flow and space

The EFSTH NNU was on the first floor of a building in the Paediatric Department complex, separated from the EFSTH Maternity Unit and main hospital by a road. The NNU was composed of a large area

divided into three rooms, organised according to clinical need (Fig.1-10). The “critical area” was the largest room (Fig.1-11), where all newly admitted neonates were assessed and stabilised, alongside neonates requiring high dependency care and more intensive monitoring. Neonates moved from the critical area to the “stable area” as their clinical condition improved and once they no longer required oxygen or intravenous fluids. The “infection control area” or septic ward was reserved for neonates with potentially infectious conditions, such as cellulitis, abscesses, infected wounds, and tetanus. However, due to the limited numbers of oxygen concentrators (Table 1-3) potentially infected patients requiring oxygen therapy were managed in the “critical area”. Inborn (born at EFSTH maternity unit) and out-born (born elsewhere, including home) neonates were not routinely separated following admission.

Figure 1-10. Floor plan of EFSTH NNU showing typical flow for neonates <2000g at PhD onset



Key: 1) Admission procedures performed whilst on “admission radiant heater”; 2) Transferred to incubator once condition stabilised, although may still require oxygen and/or IV fluids; 3) Transferred to stable area once no longer requiring oxygen and IV fluids, with subsequent discharge home

Figure 1-11. Critical ward at EFSTH neonatal unit

Source: H.Brotherton with consent

1.6.2.3.2 Human resources & training

Medical staffing comprised of one senior doctor (Consultant level, from the Cuban Medical Cadre), two medical officers and 5 to 6 junior house officers (within two years of medical school graduation). Ward rounds were conducted daily except for at weekends and an on-call rota ensured at least one medical officer and two to three house officers were always available on-site. A Consultant Paediatrician was always available, non-resident from 4pm to 9am and at weekends. At least one trained nurse (registered or enrolled nurses) worked exclusively on the NNU per shift, usually with two trained nurses during the day shift (08:00 – 20:00) and one or two nursing assistants. Only one trained nurse and one nursing assistant were present during the night shift (20:00 – 08:00). It was hospital policy to rotate nurses and junior house officers between departments, although senior staff including the neonatal lead nurse, matron, and some medical officers, had been stationed on the NNU for several years. In-house departmental training for medical staff took place weekly with consultant level input and occasionally in conjunction with visiting foreign medical personnel. New junior house officers underwent induction training at commencement of new postings in the department.

1.6.2.3.3 Equipment and monitoring

Neonates <2000g were managed either under a non-servo controlled radiant heater or in an incubator, with cots available for larger neonates (Table 1-3). Co-habitation was common, especially on the radiant heaters in the area closest to the nurses' desk, which was prioritised for those requiring frequent monitoring, resuscitation, or oxygen (Fig.1-12).

Figure 1-12. Radiant heater used for admission and monitoring of critically ill neonates at EFSTH neonatal unit

Source: H.Brotherton with consent

Oxygen was provided on the critical ward from three oxygen concentrators, with improvisation using three-way taps to enable maximum 6 neonates to receive oxygen from each concentrator. One flow-

splitter was available to titrate oxygen delivery and nasal prongs were used to deliver the oxygen. Head box oxygen, bubble CPAP (bCPAP), mechanical ventilation and surfactant were not available (Table 1-3).

Two each of phototherapy machines and suction machines were functional and in regular use (Table 1-3). No functional pulse oximeters were available for heart rate and oxygen saturation monitoring at the time of the site survey. Digital thermometers and bed-side glucometers were available, although the availability of blood glucose strips varied according to supply from hospital central stores.

Table 1-3. Equipment available for small and sick newborn care at EFSTH NNU at PhD onset

Equipment	Available	Functional
Incubators	11	10
Radiant heaters	5	5
Cots	26	NA
Ventilators	0	0
bCPAP	0	0
Oxygen concentrators	4	3
Oxygen flow splitter	1	1
Head box	0	0
Suction machines	2	1
Phototherapy machines	6	2
IV fluid pump	2	1
Pulse oximeters	5	0
Glucometers	6	1
Thermometers	2	2
Ambu-bags	3	2 (infant size)
Fridge for milk storage	0	0

Intravenous fluids were administered via fluid giving sets using the drops per minute method of regulating flow. One functioning fluid pump was reserved for medication or blood transfusions. Pre-mixed bags of maintenance fluid were not available, and 10% dextrose (standard type of neonatal maintenance fluid) was manually reconstituted from 5% dextrose and 50% dextrose with the addition of sodium chloride and potassium chloride as required for each patient. Ringer's lactate was also available for emergency fluid management. There was a consistent supply of IV preparations of vitamin K, ampicillin, gentamicin, ceftriaxone. ceftazidime, metronidazole, ciprofloxacin, phenobarbitone, adrenaline and aminophylline. Caffeine citrate, co-amoxiclav and meropenem were intermittently available via external donations. A fridge was available for storage of reconstituted antibiotics and prepared or opened fluid bags.

1.6.2.3.4 Investigations, observations, and anthropometry

Routine weighing of all neonates occurred three times per week using a digital scale (5g gradation) with weights documented in the medical record. Head circumference and length were not routinely recorded unless there was a clinical need (e.g., suspected hydrocephalus). Temperature was measured once or twice daily in the most unstable neonates on the critical ward and once daily for those more stable. Blood glucose was routinely measured daily for neonates receiving IV fluids or those critically unwell, with more frequent checks as requested by clinicians.

As reported previously, radiological and laboratory investigations at the site were limited.[27] Full blood count and malaria blood films were available from the EFSTH Paediatric Department laboratory, supported by MRCG. Routine biochemical investigations (urea, electrolytes, bone profile, live function tests, etc) were not available and serum bilirubin was processed at local private laboratories, upon payment by families. Wound, urine and cerebral-spinal fluid (CSF) cultures could be performed consistently by the EFSTH microbiology laboratory but blood culture using automated BACTEC9050 machine was only intermittently available, dependent on availability of BACTEC bottles.[27] HIV, hepatitis B and syphilis serology testing were available. Radiographs, cranial ultrasound, computed tomography (CT) scanning, and barium studies were also available, but the absence of portable machines limited utility in unwell neonates on oxygen.

1.6.2.3.5 Infection prevention control, including security/visitors policy

Oversight of ward cleaning was the responsibility of the nursing team, with two ward orderlies available for cleaning of the floors only. Nurses cleaned incubators, sinks and radiant heaters using Omo detergent with water and bleach. Clinical consumables such as face masks, suction catheters and oxygen nasal prongs and tubing were re-used between patients: washed with soap then disinfected by soaking in a common bucket with 0.15% chlorine (Fig.1-13). An auto-clave or steriliser was not available on the neonatal unit but a central auto-clave in the main hospital provided sterile dressing packs for wound dressings. Cleaning products were provided by the Infection Prevention Control (IPC) team, with a dedicated IPC nurse designated to the NNU. One sink per ward area (except for stable ward) was available for staff to wash their hands and a water bucket was provided for mother's hand washing. Due to geographical location in relation to the main hospital, the neonatal unit was not connected to the main hospital water supply and provision of water was erratic due to a low-pressure system and dependency on an external tank. If running water was not available, staff members or mothers brought water from an external tap in the Paediatric Department grounds to the neonatal unit using covered buckets. Liquid soap was available with occasional alcohol gel availability and hand drying facilities consisted of a re-usable towel. Disposable gloves were used routinely on handling of neonates. All persons entering the NNU had to change their shoes and staff members wore plastic slip on shoes, available at the entrance to the NNU and shared between staff members. Regular chemical fumigation took place 6-monthly, co-ordinated by the IPC unit, with all neonates relocated to an adjacent area for 48h.

Figure 1-13. Bucket used for disinfection of face masks at EFSTH neonatal unit

Source: H.Brotherton

Only one parent or caregiver per neonate was allowed to visit the NNU simultaneously in-order to prevent over-crowding and reduce infection risk. Fathers were not routinely allowed on the NNU but could enter if the mother was unable to attend to the newborn. The visitation policy was enforced by nursing staff, the infection prevention nurse and security officers, if required.

1.6.2.3.6 Support and space for mothers of admitted neonates

A 20-bed ward for mothers or carers of admitted neonates was situated 33 metres away from the NNU, enabling easy access for regular feeding and cares. Mothers had access to one shower, one toilet and two sinks. Any additional caregivers accompanying the mother slept in a room outside the maternity unit entrance, termed the "escorts shed". The hospital provided three meals a day to mothers or carers of admitted neonates, with no food or eating allowed in clinical areas.

1.6.2.3.7 Governance, audit & financing

National and local perinatal mortality review meetings and clinical/mortality audit activities were not taking place at the time of PhD onset. NNU admissions and deaths were reported internally as part of routine hospital information systems (HMIS), using paper-based reporting forms, and coordinated by the NNU matron. All medical records were paper based, with a pre-printed admission proforma including medication and weight charts.

Hospital admissions, routine medications, and medical consumables (e.g., cannulas) were provided to patients free of charge by the hospital, with families expected to buy any prescribed but out of stock medications. Basic investigations such as X-rays and ultrasound and full blood count were free at point of delivery with charges for CT scans and any investigations requested by the doctor but not available at EFSTH. Mothers were not charged for food or accommodation whilst their neonate was admitted.

1.6.3 Kangaroo mother care provision at study site

At PhD onset KMC was not included in The Gambian National Health Policy 2012– 2020[76] and there was no formal KMC programme operational at the study site or elsewhere in the country. KMC metrics were not being collected at local or national health systems level. The provision of the different components of KMC (KMC position, KMC nutrition and KMC discharge/follow-up) at EFSTH NNU is outlined below.

1.6.3.1 KMC position

At the time of PhD onset, continuous KMC was not routinely provided but mothers were encouraged to provide skin-to-skin contact for 30 minutes after feeding, once the neonate was stable and had stopped oxygen and IV fluids. This took place with mothers sitting in chairs next to the incubator or radiant heater. Specialised wrappers to secure the baby were not available and mothers placed their newborns inside their clothes or covered with a piece of material (Fig.1-14). Woollen hats were intermittently available, depending on donations. There was no formal KMC programme, guidelines, or facilities/resources to support mothers to provide continuous skin-to-skin contact. Provision of skin-to-skin contact was not routinely documented in medical records or NNU registers at this time. During the site survey observation, four stable preterm or LBW neonates were admitted to the "stable" ward, and none were receiving KMC contact, although all were being held fully clothed.

Figure 1-14. Mother holding her newborn in KMC position at EFSTH neonatal unit

Source: H.Brotherton with consent, May 2017

1.6.3.2 KMC nutrition

Supplementary feeding support was provided whilst neonates established breastfeeding, with milk administered by cups, spoons, syringes and/or gastric tubes, depending on availability. There was a ward feeding policy for the unit, but no feeding charts were available, hence the volume, type and timing of milk provided were not routinely documented. Electronic or manual breast pumps were not available and there was no designated refrigerator or process for storage of expressed breast milk. If formula milk was prescribed by a doctor it was provided either from donated ward supplies or bought by the family. It was usual practice to use formula milk if mothers were unavailable, had inadequate milk supply or known HIV infection. A donor milk bank was not established and parenteral feeding with lipid/protein formulations was not available. It was standard practice for neonates <2000g to receive folic acid, fat soluble vitamins and iron prophylaxis as per WHO guidelines.[3]

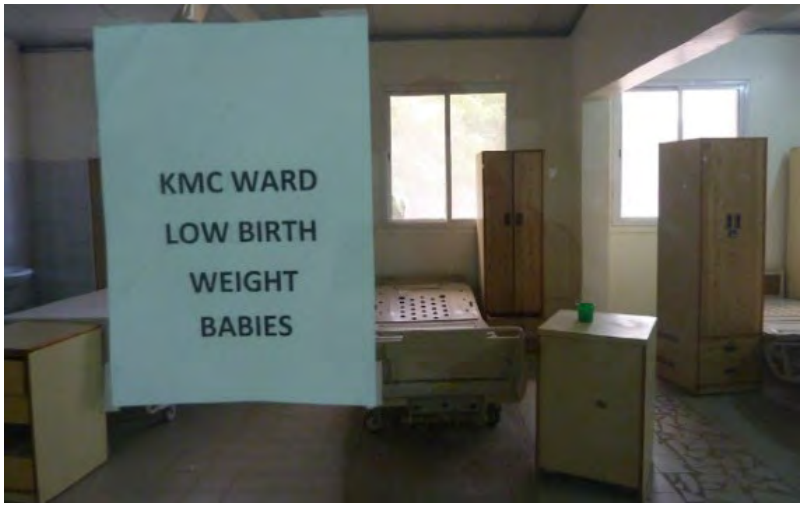
1.6.3.3 KMC discharge and follow-up

There were no formal discharge guidelines in place for preterm/LBW neonates, with discharge recommended at the discretion of the most senior doctor, and minimum criteria including weight >1.2kg, daily weight gain and clinical stability. All neonates with birth weight <1500g were followed up at a “feeding and growing” clinic with frequency determined on an individual basis and to maximum 28 postnatal days. If neonates required follow-up after 28 postnatal days they were transferred to the paediatric outpatient department. Records were not available to determine frequency of follow-up with no hospital-held registers of follow-up weights or clinical status.

1.6.3.4 Development of KMC services, training, and commitment

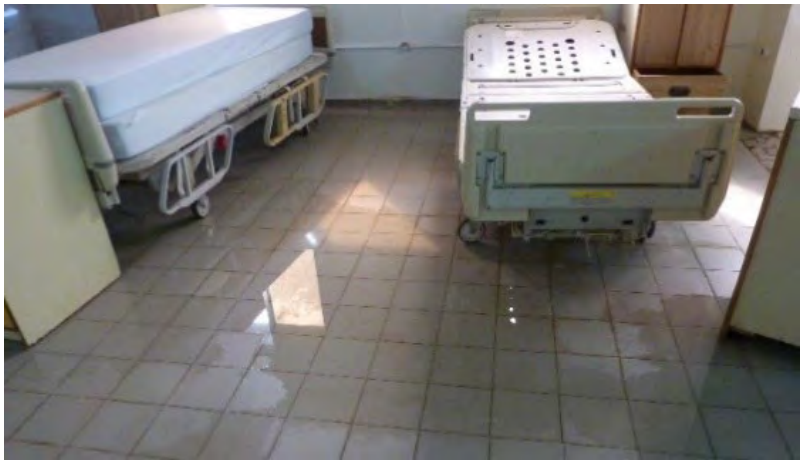
EFSTH NNU nursing staff had undergone periodic training in breastfeeding, feeding the small newborn and KMC as part of the Gambian Government Ministry of Health (GGMoH) co-ordinated Newborn Care training programme since 2014. Three nurses and the Head of Paediatric Department had participated in a UNICEF-sponsored learning visit to KMC centres in Ghana (2013) and KMC training in South Africa (2014) and were committed to implementing continuous KMC at EFSTH. Two hand-drawn posters were displayed on the NNU to promote skin-to-skin contact, suggesting NNU staff awareness and support for the practice. An unused ward (former malnutrition ward) adjacent to the NNU had been identified as a possible space for a KMC unit (Fig.1-15). Four beds, wardrobes and bedside lockers had been sourced along with gowns for mothers. Challenges hindering progress in developing the KMC unit included a leaking roof leading to flooding during the rainy season (Fig.1-16), absence of mosquito-proof windows and mosquito nets, lack of adequate WASH facilities for mothers/caregivers and limited specialised health worker training on KMC.

Figure 1-15. Room identified as a potential KMC unit at EFSTH



Source: H.Brotherton, September 2016

Figure 1-16. Potential KMC unit at EFSTH with flooded floor during rainy season



Source: H.Brotherton, September 2016

1.7. Summary of background and study setting

Global neonatal mortality remains unacceptably high with the greatest burden in small and sick newborns, especially those born preterm and SGA. Global policy has recently shifted to recognising the importance of high quality SSNC in improving newborn survival, which is critical to meet global targets over the coming decade. KMC is central to SSNC, as an entry point for improved quality and family centred care and is recommended for all stable neonates ≤2000g. However, a key evidence gap exists for use of early KMC prior to stability, which is being addressed in this PhD and other recently completed or ongoing clinical trials. At PhD onset, The Gambia had one of the highest neonatal mortality rates globally with substantial health systems limitations for delivery of high quality SSNC at the research site. KMC was not available due to infrastructure and HCW training gaps yet there was strong commitment from all stakeholders for KMC implementation and recognition of the importance of this potentially life-saving package of care.

Chapter 2 Aims, objectives & structure of the PhD

2.1. Motivation for PhD

I worked at EFSTH NNU as a paediatric registrar and RCPCH-VSO fellow from 2007 to 2009. During this time, I witnessed first-hand the unacceptably high neonatal mortality rates, predominantly due to preventable or treatable conditions yet hampered by systemic health systems limitations. This motivated me to develop skills as a clinical researcher in-order to evaluate feasible, acceptable, and low cost newborn care interventions with high potential mortality impact. During this PhD I was motivated by the power of research to improve clinical care as well as to generate high quality evidence for policy and programmatic change. My previous experiences and professional links formed at EFSTH and beyond within The Gambian health system informed my choice of study site and provided a welcome opportunity to contribute to sustainable improvements in SSNC and KMC roll-out in The Gambia.

2.2. Aim and objectives of PhD

The overall aim of this PhD was to investigate if early KMC improved survival and clinical outcomes for mild-moderately unstable neonates <2000g in a Gambian level 2/2+ NNU.

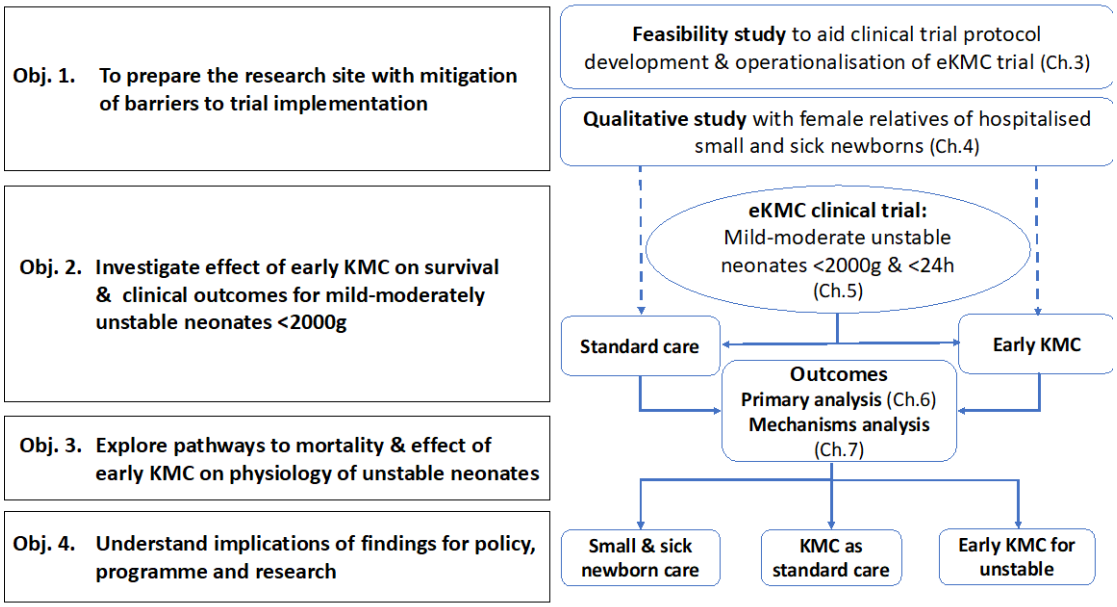
There were 4 specific objectives:

1. To prepare the research site with mitigation of barriers to trial implementation
2. To investigate the effect of early KMC on survival and other clinically important outcomes, including safety, for unstable neonates <2000g
3. To explore pathways to mortality and physiological effects of early KMC prior to stability
4. To determine the programmatic/policy and research implications of the PhD findings for SSNC, KMC as standard care and early KMC prior to stability

2.3. Structure of thesis

This thesis is framed around three research studies: 1) A feasibility study to identify barriers to clinical trial implementation and conduct; 2) A qualitative study to understand female relative's perceptions towards KMC and 3) An individually randomised controlled trial (Fig.2-1).

Figure 2-1. PhD thesis framework and structure, as per PhD objectives



This thesis comprises of a combination of traditional chapters and three research articles published in peer-reviewed journals. An overview of the thesis is provided below:

Chapter 1 gives an overview of the global burden of neonatal and preterm mortality with discussion of key definitions and concepts. This is followed by presentation of evidence and practice for KMC as standard care and the rationale for investigating use of early KMC prior to stability. The Gambian context and study site is described in detail, with focus on SSNC and KMC provision at time of PhD onset.

Chapter 2 outlines the aims, objectives, motivation, and structure of the PhD with information about funding, ethical and regulatory approvals, and the candidates' contributions to the thesis. A detailed timeline for the PhD is also presented (Annex A-1).

Chapter 3 addresses Objective 1 by describing the preparations required at the research site to conduct the eKMC trial. This included improvements to SSNC, implementation of KMC as standard care and trial-specific preparation for site alterations to enable provision of the intervention. A feasibility study was also conducted to identify recruitment barriers and inform trial protocol development.

Chapter 4 addresses Objective 1 by exploring the perceptions towards KMC amongst Gambian female relatives of hospitalised neonates <2000g. This was important to overcome anticipated recruitment barriers and to gain insights from this key stakeholder group with wider relevance to SSNC and KMC programmes in LMIC settings. This chapter was published in a peer-reviewed journal (Qualitative Health Research).

Chapter 5 addresses Objective 2 and provides a detailed account of the methods for a single-site individually randomised controlled trial aiming to investigate the 28-day mortality and clinical effects

of early KMC in unstable neonates <2000g (eKMC clinical trial). Chapter 5 has been published in a peer-reviewed journal (Trials).

Chapter 6 addresses Objective 2 and presents the primary analysis of the eKMC trial, with reporting of the primary and secondary outcome/safety data and consideration of the findings in the context of existing evidence for early KMC in unstable neonates. This chapter has been published in a peer-reviewed journal (The Lancet's EClinicalMedicine).

Chapter 7 addresses Objective 3 by reviewing the evidence for pathways to mortality for preterm neonates and mechanisms of effect for KMC, with synthesis into an original conceptual framework to explore the effect of early KMC on pathways to mortality. Exploratory analyses of eKMC trial data are then presented to understand changes to mortality at the research site during the trial period, pathways to mortality within the eKMC trial cohort and the effect of early KMC on selected physiological factors over the first 24h of enrolment. The results of these exploratory analyses are discussed considering the existing evidence, with consideration of the strengths and limitations of this research.

Chapter 8 provides a detailed interpretation of the main findings of the preceding chapters (3-7), in the light of existing literature especially the recent findings from the iKMC trial. I also reflect on the eKMC trial pragmatic design as well as recruitment and ethical challenges associated with conducting emergency care research with a time-limited intervention. Strengths and limitations of the PhD as a whole are also discussed.

Chapter 9 addresses Objective 4 and outlines the implications of this PhD for programme, policy, and future research, considering the themes of SSNC, KMC as standard care and early KMC prior to stability. The overall PhD conclusion is presented here.

2.4. Ethical and regulatory approvals

All research presented in this thesis received ethical approval from LSHTM observational or interventional Ethics Committees and the Gambian Government/Joint MRCG Ethics Committee. In addition, the MRCG Scientific Co-ordinating Committee (MRCG-SCC) provided scientific overview and approval of the study proposals/protocols and the Gambian Government Ministry of Health (GGMoH) approved conduct of all studies. As sponsor of the eKMC trial, the LSHTM Clinical Governance Office provided institutional oversight and quality assurance with delegation of local safety monitoring to MRCG Clinical Trials Support Office. Details of the regulatory approvals are outlined in Table 2-1 with institutional and ethical committee approval letters included in Annex A-1.

Table 2-1. Overview of ethical approvals and regulatory oversight for research

Chapter	Title of study	LSHTM EC reference & date of initial approval	GG/MRCG EC reference & date of approval	Other regulatory approvals	Annex
3	An investigation of early KMC for hospitalised neonates <2000g: A feasibility study	Ref: 11887 27th Feb 2017	SCC: 1503 12th Oct 2016	GGMoH	A-1-1 A-1-2 A-1-3
4	Acceptability of female family members as potential substitute kangaroo care providers in The Gambia	Ref: 12398 21st June 2017	SCC: 1535 21st April 2017	EFSTH (study site)	A-1-4 A-1-5 A-1-6
5, 6 & 7	A randomised controlled trial of early continuous KMC versus standard care on survival of hospitalised unstable neonates <2000g in The Gambia	Ref: 14545 26th Feb 2018	SCC: 1591 19th Mar 2018	GGMoH LSHTM as sponsor	A-1-7 A-1-8 A-1-9 A-1-10

Abbreviations: EC = Ethics Committee; g = grams; GGMoH = Gambian Government Ministry of Health; GG/MRCG = Gambian Government / Medical Research Council Unit The Gambia at LSHTM; KMC = Kangaroo Mother Care; LSHTM = London School of Hygiene & Tropical Medicine; Ref = reference from LSHTM Ethics Committee; SCC = Scientific Co-ordinating Committee at MRCG

2.5. Funding

The research presented in this PhD was funded by a Wellcome Trust Research Training Fellowship (Ref: 200116/Z/15/Z); 26th August 2016 – 6th August 2021). This included funding for all costs associated with the research and to enable residence for myself and my family in The Gambia (January 2017 – September 2020). A LSHTM travel grant was awarded to Maura Daly (MsC student) to enable her to travel to The Gambia for the data collection period of the qualitative study exploring perceptions of female relatives towards KMC.

2.6. Role and contributions of the candidate

I led the conceptualisation of all work in this thesis, in collaboration with my lead supervisor, Prof. Joy Lawn. I designed the feasibility study and oversaw data collection by the field team whilst leading the site preparation activities, including implementation of KMC as standard care and development of standardised guidelines. Many other people were involved in the site preparation activities and a detailed breakdown is provided in Table 2-2. For the qualitative study of female relatives' perceptions, I supervised Maura Daly, LSHTM MsC student, and provided intellectual input to study design, development of data collection tools, interpretation of data and led the manuscript writing and development leading to publication of this work. As principal investigator (PI) of eKMC clinical trial, I wrote the trial protocol with input from my supervisors and PhD advisory committee and led the field team in the implementation of the trial. I provided oversight and co-ordination of regulatory and ethical approvals, liaising with the sponsor, trial monitors, Data Safety Monitoring Board (DSMB) and Trial Steering Committee (TSC), along with supervising and inputting to the development of the data collection tools and study specific procedure (SSPs). I maintained oversight of the field team activities, with delegation and supportive supervision of responsible persons during trial conduct. I performed all statistical analyses presented in this thesis with support from Abdul Khalie Mohammad (MRCG) and Prof. Simon Cousens (LSHTM). I wrote this thesis and prepared all figures unless otherwise stated.

Table 2-2. Contributions by the candidate and other colleagues to work presented in this thesis

#	Chapter	Activity	Responsibility	Additional input/oversight
1	Background	Conceptualisation & writing	**H Brotherton**	Review by: JE Lawn, Cally Tann, Wariri Ohgenbruhe
2	Aims, objectives & structure	Conceptualisation & writing	**H Brotherton**	JE Lawn, A Roca, CJ Tann, S Cousens
3	Preparing to conduct a clinical trial of early KMC for unstable neonates <2000g	Conceptualisation and preparation of Wellcome Trust funding application	**H Brotherton**, JE Lawn	SA Zaman
		Preterm/LBW guideline development	**H Brotherton**, A Gai	Review by: C Ilacer
		EFSTH environmental surveillance data collection & processing	M Jallow, S Darboe, B Ceesay	**H Brotherton**
		KMC implementation as standard care	**H Brotherton,** A Gai, L Camara, E Keita, C Ilacer, R Paulinho	M Janneh (UNICEF The Gambia); F Fatty & F Camara (GGMoH)
		KMC progress monitoring data collection	**H Brotherton, A Gai,** S Kapoor	
		Feasibility study design	**H Brotherton**, JE Lawn, SA Zaman	S Cousens, CJ Tann, A Seale, C Bottomley
		Feasibility study data collection	B Kebbeh, R Bojang, B Jarju	**H Brotherton,** E Quesada Gonzalez
		Feasibility study analysis	**H Brotherton**	JE Lawn, SA Zaman
		Write-up of chapter	**H Brotherton**	Review by: A Roca, CJ Tann, S Cousens, JE Lawn
4	"We all join hands" Perceptions of the kangaroo method among female relatives of newborns in The Gambia (Paper A)	Conceptualisation of study	**H Brotherton**, M Daly	JE Lawn
		Design of study data, collection tools & interview guides	M Daly, **H Brotherton**	L Penn-Kekana
		Coordination & conduct of interviews	M Daly, B Jarju	**H Brotherton**
		Analysis & interpretation of data	M Daly	**H Brotherton**, L Penn-Kekana
		Drafting of manuscript	**H Brotherton,** M Daly	Review by: JE Lawn, J Schellenberg, L Penn-Kekana, P Johm
		Review of drafts and approval of final version	All authors	
5	Protocol for a randomised trial of early Kangaroo mother care compared to standard care on survival of pre-stabilised preterm	Conceptualisation of trial	**H Brotherton**, JE Lawn	S Cousens
		Trial design & drafting of trial protocol	**H Brotherton**	JE Lawn, SA Zaman, S Cousens, A Roca, CJ Tann, A Seale
		Preparation of case report forms and SOPs	**H Brotherton,** A Gai, Y Njie, S Darboe	A Roca, UN Nakakana, V Thomas-Njie
		Protocol implementation	**H Brotherton,** A Gai, B Kebbeh, G Walker	A Roca, AL Samateh

	neonates in The Gambia (eKMC)(Paper B)	Drafting of manuscript	**H Brotherton**	Review by: JE Lawn, A Roca, S Cousens, CJ Tann, A Seale
		Review of drafts and approval of final version	All authors	
6	Impact of early kangaroo mother care versus standard care on survival of mild-moderately unstable neonates <2000g: A Randomised Controlled trial (Paper C)	Participant screening, recruitment, data collection and follow-up. Quality checks/data cleaning Community sensitisation	Delegated to: A Gai, G Walker, B Kebbeh, R Bojang, F Jarju, N Samba, S Sanyang, M Sey, M John, T Sonko, M Fatty, J Kebbeh, F Darboe	**H Brotherton**
		Microbiological sample processing, reporting & storage	S Darboe, M Jallow, B Ceesay, D Cham	**H Brotherton**
		Coordination of data cleaning & management of electronic databases	Y Njie, B Saidy, J Jones	BL Dondeh, **H Brotherton**
		Monitoring of trial conduct against ICH-GCP standards and quality assurance	G Sey, M Heffner, F Joof	V Thomas Njie, P Henley
		Reporting of serious adverse events & protocol deviations to sponsor, DSMB and ECs	**H Brotherton,** A Gai	A Roca, V Thomas Njie
		Oversight of trial conduct & progress, including co-ordination of ethical and regulatory approvals	**H Brotherton, A Roca, JE Lawn**	S Cousens, CJ Tann, E Carrol, E Mason, D Elbourne, J Crawley, C Ezeaka, B Abatan
		Analysis	**H Brotherton**, AK Mohammad	JE Lawn, A Roca, S Cousens
		Drafting of manuscript	**H Brotherton**	Review by: JE Lawn, A Roca, S Cousens, CJ Tann
		Review of drafts and approval of final version	**H Brotherton,** All authors	Review by: E Carrol, E Mason, D Elbourne, J Crawley
7	Pathways to mortality and physiological effects of early KMC amongst unstable neonates <2000g	Conceptualisation	**H Brotherton**, JE Lawn	A Roca, S Cousens, CJ Tann
		Data collection of prospective in-patient mortality data	A Gai, G Walker, B Kebbeh, R Bojang, F Jarju, N Samba, S Sanyang, M Sey, M John, T Sonko, M Fatty, J Kebbeh	**H Brotherton**
		Analysis of mechanisms data from eKMC trial	**H Brotherton**	S Cousens, A Roca
		Writing of chapter	**H Brotherton**	Review by: JE Lawn, A Roca, S Cousens, CJ Tann, M Medvedev
8	Discussion	Conceptualisation & writing	**H Brotherton**	Review by: JE Lawn, A Roca, S Cousens, CJ Tann
9	Implications & conclusion	Conceptualisation & writing	**H Brotherton**	Review by: JE Lawn, A Roca, S Cousens, CJ Tann

2.7. PhD timeline

The research training fellowship and PhD began in September 2016 with the initial site survey and a period undergoing clinical trials training at LSHTM. There was then a 2 month delay to planned relocation to The Gambia and commencement of the feasibility/preparation field work due to an unexpected political impasse in The Gambia. Hence, field work was conducted from February 2017 to April 2020 with the first 15 months focused on site preparation and mitigation of trial implementation barriers (PhD objective 1). Objective 2 spanned the whole PhD period, with eKMC trial protocol development running parallel to preparation/feasibility activities followed by conduct of the eKMC trial from May 2018 to April 2020. There was a 5-month "interruption of studies" period from April to September 2020 when I supported the MRCG COVID-19 clinical and leadership response. I then conducted the eKMC trial analysis, exploratory analyses and completed the PhD write-up from September 2020 to August 2021 (Annex A-2).

PhD OBJECTIVE 1:

To prepare the research site with mitigation of barriers to trial implementation

Source: Louis Leeson/LSHTM, 2019. Reproduced with permission

Chapter 3 - Preparing to conduct a clinical trial of early kangaroo mother care for unstable neonates <2000g

3.1. Scope of the chapter

This chapter describes the processes and activities involved in preparing the study site for the eKMC clinical trial, with consideration of changes to SSNC, implementation of KMC as standard care and a feasibility study to inform trial protocol development and intervention delivery (Table 3-1). A framework to guide collection of process and implementation data and to inform understanding of early KMC delivery was developed during this phase and is also presented in this chapter.

Table 3-1. Operationalisation of the eKMC clinical trial protocol

	Feature of eKMC trial protocol	**Activities undertaken to prepare for eKMC trial**	**Outcome of preparation**
Small and sick newborn care	The intervention & outcomes are unblinded for participants, HCWs & research team	- Clinical guidelines for SSNC developed & implemented - Clinical guidelines included in trial SSPs	Reduced risk of performance bias with compliance monitoring
	Clinically suspected infections are a secondary outcome & likely contributor to mortality	- Environmental surveillance at baseline - Activities to address IPC gaps	Insights into changes to context of environmental exposures & risk of HAI during the trial
KMC for stable	Intervention and control definitions both include continuous KMC, albeit at different timings & stability levels	- 8-bed KMC unit established - HCW training on KMC theory & practice - Supportive supervision	Continuous KMC established as standard care for stable neonates <2000g
eKMC trial protocol development	Population: Unstable neonates aged <24h & <2000g Intervention: KMC within 24h of admission Control: Standard care Outcome: 28-day mortality	- Feasibility study to understand the target population, feasibility of recruitment & local data for baseline mortality - Internal pilot phase to trial data collection tools and study specific procedures	1. Barriers to recruitment identified 2. Study procedures & definitions refined 3. Sample size calculated with assessment of recruitment feasibility
Early KMC for unstable	Early KMC will be provided to unstable neonates <2000g within 24h of admission	- Alterations to NNU environment (beds; infra-structure; patient flow; equipment) - Sensitisation & training of HCW on KMC for unstable neonates - Sensitisation of pregnant women & communities about the trial	4. Female relatives identified as key for intervention delivery 5. Continuous early KMC provided to unstable neonate

Abbreviations: HAI = Hospital acquired infections: HCW = Health care worker; IPC = Infection prevention control; KMC = Kangaroo mother care; NNU = Neonatal unit; SSNC = Small and sick newborn care; SSP = Study specific procedure

3.2. Changes to small and sick newborn care

3.2.1 Standardised clinical guidelines for small and sick newborn care

Due to the nature of the intervention, the eKMC trial was designed as a non-blinded randomised controlled trial (RCT). Thus, there was a high risk of performance bias due to potential for systematic differences in other management[77] with possible sub-conscious bias favouring the intervention due to KMC being an established package of care for stable neonates. This risk was mitigated by developing, implementing, and training HCW and research personnel on a clinical guideline to provide standardised SSNC to both trial arms in all domains apart from timing of KMC initiation. The guideline was developed in collaboration with EFSTH senior neonatal doctors and was based on existing standard care with adaptations to ensure consistency with WHO guidelines.[3, 42] It addressed all aspects of routine and emergency SSNC, including thermal and glycaemic control, management of respiratory compromise, feeding/nutrition (including use of gastric tube feeds), resuscitation and infection prevention and management. Criteria for prophylactic antibiotics use was also included, with first line choice of Benzylpenicillin and Gentamicin for all neonates <2000g. This was based on usual care, with the recognition that accurate history of perinatal septic risk factors is frequently not available at time of admission and untreated early onset neonatal infection can be rapidly progressive with limited supportive treatment options available locally.

The clinical guideline also formalised and facilitated the use of bCPAP in the management of neonatal respiratory distress. The EFSTH medical team introduced bCPAP in 2017 in partnership with Humanity First, a medical and humanitarian NGO. However, the three donated Diamedica bCPAP machines were inconsistently used until mid-2018, when existing guidance about when and how to use bCPAP was incorporated into the eKMC trial SSNC guideline and associated training sessions. This was necessary for the eKMC trial as bCPAP is an important newborn intervention associated with 66% reduced risk of mortality[78] and ensuring standardised use across the trial treatment groups was essential to avoid performance bias.

Extensive training on the guideline was conducted with both EFSTH HCW and MRCG research personnel during 2017 and 2018, with refresher training at periodic intervals until 2020. For consistency, guideline content was incorporated into the participant and trainer manuals for the GGMoH/UNICEF care of the small newborn and KMC training programme, with national and local trainings in 2017 and 2018 (Fig. 3-1, Table 3-2).

The SSNC guideline was incorporated into eKMC study specific procedures with a plan for daily compliance assessments detailed in the trial protocol (Chapter 5). Training was repeated with EFSTH staff as required and at the induction of new junior clinicians and in response to major deviations from the guidelines.

Figure 3-1. Participants and facilitators at the national training of trainers workshop on 'Care of the small baby and KMC'

Source. H.Brotherton, with consent, August 2017

Table 3-2. Health care worker training on SSNC and KMC linked to trial implementation

Dates	Training session	Number/cadre of trained HCWs
9 health facilities across all regions in The Gambia (inc. EFSTH)		
August 2017	National "Care of Small Newborn & KMC" Training of Trainers workshop 4 day workshop x 1	Nurses/midwives (20), medical officers (3) & programme managers from GGMoH (2)[a]
EFSTH nursing, midwives & doctors		
August & September 2017	Step-down training 2 day workshops x 3	Medical officers (5) Consultant paediatrician (1) Trained nurses (12) Midwives (9) Nursing assistants (12) Infection prevention nurse (1)
March 2018	Step-down "Care of Small Newborn & KMC" workshop 4 day workshops x 2	Trained nurses (14) Nursing assistants (32) Medical officers (4) MRCG research nurses (5)
eKMC trial team (nurses/doctors)		
April 2018 – December 2019	Standardised guideline for SSNC 1 day training every 3 – 6 months (4 days total)	MRCG research nurses (7) MRCG research clinicians (2)

a) 14 HCW identified as trainers for step-down KMC training

Abbreviations: EFSTH = Edward Francis Small Teaching Hospital; GGMoH = Gambian Government Ministry of Health; HCW = Health care workers; KMC = Kangaroo mother care; MRCG = Medical Research Council Unit The Gambia at LSHTM; SSNC = Small and Sick Newborn Care

3.2.2 Environmental surveillance & infection prevention control activities

3.2.2.1 Methods for environmental surveillance activities

We anticipated that trial related activities could lead to changes in infection control practices and potentially alter the burden of environmental bacteria at the site, possibly impacting on the trial outcomes of infections and mortality. Environmental surveillance activities were conducted prior to recruitment commencing (8th May 2018) and at 5 to 7-monthly intervals with the last samples collected 6-months prior to trial cessation. The surveillance comprised of sampling the following domains: frequently touched surfaces; medical equipment (suction machine, bCPAP, oxygen concentrators); patients' immediate surroundings (incubators/radiant heaters); ward sinks and toilets and opened/unopened antibiotics and fluids. The surveillance included all clinical areas to which study participants would be potentially exposed (critical ward; trial area and KMC unit) and was conducted according to a standard procedure, consistent with previous outbreak investigations at the site.[79] Cotton swabs were used to obtain surface samples with specimens from liquid sources obtained aseptically.

All samples were processed at MRCG Clinical Laboratory according to standard department procedures for bacteriology. Liquid specimens (e.g., fluid, and antibiotic specimens) were inoculated into BACTEC Peds Plus/F bottles and processed in BACTEC 9050 BD machine, with sub-culture of positive isolates as per standard bacteriology protocols. Antibiotic susceptibility testing was undertaken for clinically relevant isolates only according to CLSI 2017 standards[80] with detection of Extended Spectrum Beta Lactamases (ESBL) using the double disc synergy test using a third-generation cephalosporin and amoxicillin-clavulanate disc.

3.2.2.2 Results & actions for baseline environmental surveillance

Two-thirds (20/47, 64%) of environmental samples isolated a potential pathogen with mixed growth in 80% (16/20) of positive samples. Important negative samples included: nurses desk surface; doctors' stethoscope; re-usable oxygen cannulas and all antibiotic vials (opened and unopened) and sterile (unopened) fluid bags. Bacillus spp. and Staphylococcus spp. were identified from many frequently touched surfaces and re-usable consumables, including: ward round and equipment trolleys; radiant heaters; incubators; interior of antibiotic storage fridge; water from staff bathroom and oxygen concentrator; sinks; re-usable ambu-bags, suction catheter and bCPAP prongs.

Pathogenic gram-negative bacteria (GNB) were isolated from 28% (13/47) of samples, with 4/14 (29%) of ESBL-producing *Klebsiella pneumoniae* isolates identified. The sources of the ESBL-*Klebsiella pneumoniae* included the suction machine catheter, water container used for mother's hand washing, the surface of the KMC Unit sink and the bucket used to sterilise re-usable face masks used during resuscitation. Opened potassium chloride vials and sodium chloride/ringers lactate fluid bags were contaminated with *Burkholderia cepacia* or *Pseudomonas spp*. The bCPAP and oxygen concentrator water containers were also contaminated with *Pseudomonas spp*. (Table 3-3).

Table 3-3. Baseline environmental surveillance findings at study site, with linked infection prevention control activities

Sample	Gram-negative bacteria	Actions taken to mitigate HAI risk
10% Potassium chloride vial[a]	Burkholderia cepacia	Disposable 50ml syringes sourced & made available IV fluid preparation checklist developed HCW training on checklist & refresher training at new staff inductions
Normal saline bag[a]	Burkholderia cepacia	
Ringer's lactate bag[a]	Pseudomonas spp	
Liquid soap	Pseudomonas spp	Central liquid soap supply checked (no growth)
Oxygen concentrator	Pseudomonas spp	Water containers cleaned with bleach & sterile distilled water used to re-fill between patients
bCPAP machine (water)	Pseudomonas spp	
Suction catheter	Coliform spp (ESBL+)	New suction machine provided Machine cleaned with bleach/chlorine daily Second tubing identified and cleaned with bleach
Suction machine fluid container	Klebsiella spp	
Face mask sterilising container	Klebsiella spp (ESBL+)	New bucket provided with change to cleaning re-usable items on NNU sinks instead of staff toilet sinks
KMC unit sink	Klebsiella spp (ESBL+)	Cleaned with bleach daily
Critical ward sink	Coliform spp	Cleaned with bleach daily
Mothers' water container for hand washing	Klebsiella spp (ESBL+)	New bucket provided, cleaned weekly with bleach Liaison and advocacy with hospital management to provide consistent supply of running water
Ward round trolley	Coliform spp	Cleaned with bleach daily
Equipment cabinet	Coliform spp	Cleaned with bleach daily

a)Opened vials/ fluid bag. A sample of the unopened vials/fluid bags in the storeroom was also tested and no growth was identified.
Abbreviations: bCPAP = Bubble Continuous Positive Airway Pressure; ESBL = Extended Spectrum Beta Lactamase; HCW = Health Care Worker; IV = Intravenous fluids; KMC = Kangaroo Mother Care; NNU = Neonatal Unit; spp = species

A multi-stakeholder participatory approach was taken to address the findings of the baseline environmental surveillance, with involvement of the IPC department, Paediatric Department, hospital administrators and MRCG clinical laboratory and researchers. The working group highlighted several factors which may have contributed towards the environmental contamination, including: inconsistent supply of running water; re-use of 50ml syringes and needles during IV fluid preparation; lack of refrigeration of prepared fluids; and cleaning of consumables in the staff washroom prior to chemical disinfection. Appropriate actions were taken to address these findings (Table 3-3) with subsequent 6-monthly monitoring of environmental bacterial presence. Contaminated IV fluids were not detected again during the eKMC trial period, and no ESBL-producing isolates were detected from any source 6-months later (October 2018, Annex A-3). However, over time highly pathogenic bacteria such as *Burkholderia cepacia*, *Acinetobacter spp*. and *Pseudomonas spp*. continued to be identified at different sources on the NNU, principally linked to water reservoirs in equipment (bCPAP/oxygen concentrators, suction machine) and sinks/water containers for hand washing. Further efforts were made by EFSTH NNU team to address IPC within the confines of the resources available and a new water tank and pump was installed at the NNU in January 2019 (Annex A-3).

3.3. Establishing KMC as standard care for stable newborns

In the sub-sections below, I will give a summary of the rationale for establishing KMC as standard care for stable newborns before trial onset, along with a description of the stakeholders involved, activities co-ordinated by the KMC taskforce and timelines. Progress in KMC implementation was objectively tracked from PhD onset to objectively measure changes at the site using a validated tool,[75] the results of which are also presented below.

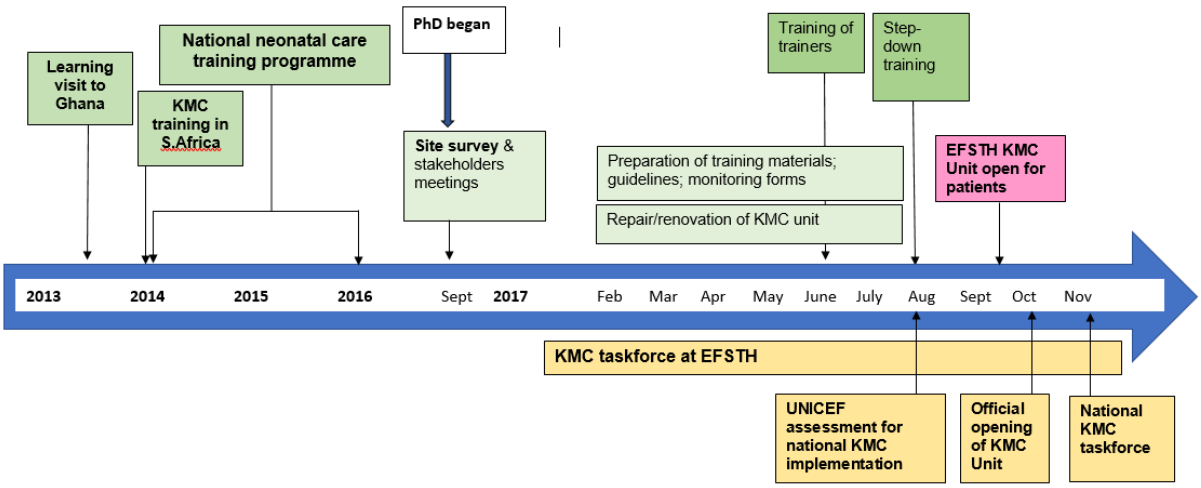
3.3.1 Rationale for establishing KMC as standard care

Continuous KMC was not practised at EFSTH NNU before PhD onset[27] but there was commitment from senior HCW and a dedicated space available (Chapter 1). KMC provision for stable newborns was needed for operationalisation of the planned clinical trial as well as acceptance of the intervention by EFSTH HCW. It was also ethically necessary to bring the control arm and standard care in line with current international guidelines, as KMC is recommended for all stable neonates ≤2000g.[42]

3.3.2 Timeline for KMC set-up at the study site

The KMC implementation process started in February 2017 and lasted 7 months with the first patient admitted to the EFSTH KMC Unit on 21st September 2017. The implementation built on a foundation of previous training and commitment by GGMoH and EFSTH senior medical and nursing staff, including national GGMoH training on care of the small preterm and KMC which was conducted regularly from 2014 (Fig.3-2).

Figure 3-2. Timeline and overview of KMC implementation at EFSTH neonatal unit, in relation to PhD onset

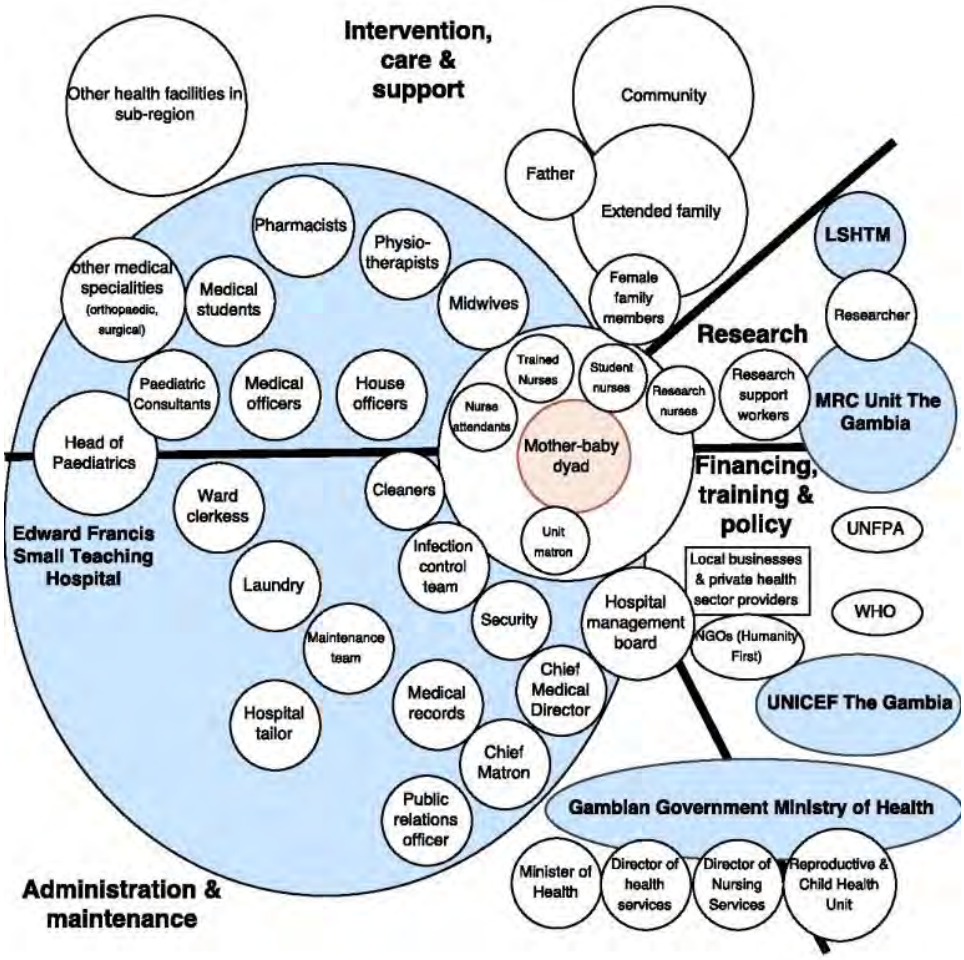


Abbreviations: EFSTH = Edward Francis Small Teaching Hospital; KMC = Kangaroo Mother care; UNICEF = United Nations International Children's Emergency Fund.

3.3.3 Stakeholders involved in KMC set-up

A local KMC taskforce was established with representation from all major partners: GGMoH; EFSTH Paediatric Department senior nursing/medical personnel; MRCG at LSHTM and UNICEF The Gambia. Other stakeholders were involved as needed, including EFSTH security department, hospital tailors, medical records, and maintenance department, as well as local businesses who were approached for additional funding (Fig 3-3).

Figure 3-3. Stakeholders involved in implementation of continuous kangaroo mother care at EFSTH



Key: Blue shaded circles indicate major partners involved in the KMC implementation process at EFSTH NNU.
Source: Adapted from Bergh et al, 2002.[45]
Abbreviations: LSHTM = London School of Hygiene and Tropical Medicine; NGO = Non-Governmental organisations; UNFPA = United Nations Population Fund; UNICEF = United Nations International Children's Emergency Fund; WHO = World Health Organisation.

3.3.4 Activities to establish KMC as standard care for stable newborns <2000g

A 'pedestal' approach was taken to implementation, with exclusive focus on KMC as opposed to embedding it within other newborn care packages.

The local KMC taskforce undertook a range of activities, based on existing evidence of health-system bottle necks,[62] barriers and enablers for KMC roll-out and implementation guidance[45] aiming to establish continuous KMC as standard care at EFSTH (Table 3-4). UNICEF-The Gambia sponsored a KMC expert (Dr Elise Van Rooyen, Kalafong University Hospital, Pretoria, South Africa) to visit The Gambia to conduct a situational analysis for national KMC implementation, which enabled expert input to the implementation process at EFSTH. The intention was to establish EFSTH as a centre of excellence for KMC, with national KMC roll-out at other facilities linked to this process.

Table 3-4. Activities undertaken by local KMC taskforce to implement continuous KMC as standard care for neonates ≤2000g at EFSTH neonatal unit

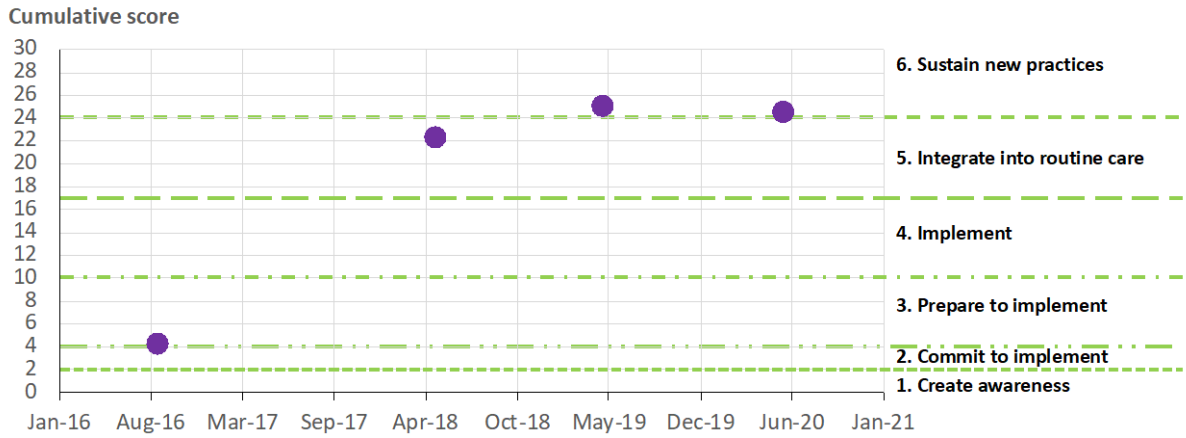
Objectives	Activities	Outcomes
Provide a safe and respectful environment for provision of continuous KMC (including follow-up)	- Funds secured from external donors - Repair of KMC unit roof & mosquito netting on windows - Sourcing of extra beds and pillows with waterproof covers, sheets, and mosquito nets - Sourcing of comfortable rocking chairs - Preparation of clinic room for KMC follow-up - Construction of lockers for safe storage of KMC provider's belongings - Renovation of KMC unit WASH facilities (toilet/shower/sinks) - Provision of buckets for sterilising of feeding aids using chemical methods (Milton) - Refrigerator for storage of expressed milk - Kettle for use by KMC mothers - Television/DVD player for KMC clinic room with KMC educational & recreational DVDs - Installation of curtains to ensure privacy - KMC wrappers made by hospital tailors with sustainable system for material availability[b]	8[a] bed KMC unit with clinic room attached Private and comfortable environment with recreational activities Toilet and shower for exclusive use by KMC providers Facilities to enable hand hygiene & safe milk storage/feeding
Ensure mothers have support to provide continuous KMC[c]	- Plan for mothers to always have 1 helper (family member) with them - Neonatal unit security & access policies reviewed and updated - Direct engagement with EFSTH security team to explain changes to policy - Peer-to-peer support system with 'Alkalo-mother'[c] identified to support other mothers	Mother plus 1 helper allowed unrestricted access to KMC unit Family & peer support encouraged
Provide evidence based KMC	- Development of comprehensive KMC guidelines, including feeding support, admission, and discharge criteria	Guidelines introduced with visual job aids
Ensure NNU personnel have skills and knowledge to support KMC provision	- Development of participant & facilitator training manuals - National Training of Trainers workshop (2017) - Local cascade training for EFSTH HCW (2017) - KMC learning visit to Lebanon for 3 NNU HCW[d] - Refresher training for EFSTH paediatric & maternity unit HCW (2018) - Supportive supervision from Consultant Paediatrician[e] and senior medical officer	High quality training on SSNC and KMC provided to 40 EFSTH HCW Supportive supervision during KMC unit set-up & beyond
Establish a method of measuring KMC coverage to inform service development	- Designed and printed KMC unit register for collection of routine admission/discharge data, including follow-up attendance and weights - Designed and introduced in-patient monitoring forms to document vital signs, feeding & KMC duration	KMC unit register, and monitoring forms embedded into KMC unit practice
Sensitise the wider community about importance and benefits of KMC	- Official opening of KMC unit, with high level Gambian government speakers and media coverage - Annual sensitisation events on World Prematurity Day - Engagement with prominent Gambian leaders to support the KMC unit and provide media coverage	Gambian community becoming familiar with concept of KMC, and profile of preterm neonates raised on the national health policy agenda

a) The KMC unit was initially opened as a 6-bed unit on 11th October 2017, but 2 beds were added in 2018 prior to the start of eKMC trial, due to high clinical demand; b) Mothers were provided with a pre-made KMC wrapper and asked to provide 2m of material at the time of discharge or follow-up, used by hospital tailors to make more wrappers; C) Alkalo is the Mandinka (local language) term for community leader. One 'Alkalo' KMC provider was identified by HCW, who then supported and organised other mothers on the KMC unit; d) A UNICEF-funded learning visit to Lebanon was attended by the NNU matron, a long-standing nursing assistant and a senior medical officer, all of whom were on the local KMC taskforce; e) PhD candidate
Abbreviations: EFSTH = Edward Francis Small Teaching Hospital; HCW = Health care workers; KMC = Kangaroo Mother care; NNU = Neonatal unit; UNICEF = United Nations International Children's Emergency Fund; WASH = Water Sanitation & Hygiene

3.3.5 Tracking progress in KMC implementation during PhD

Tracking progress in KMC implementation is important for monitoring KMC scale up at the local and national health systems level. The Stages of Change KMC health facility assessment tool has been used to evaluate national KMC implementation across health facilities[75] but is also suitable for single health facility assessments and has been assessed in >65 hospitals, including West Africa.[81] The stages of change are defined as 6 consecutive levels ranging from: 1. Creating awareness by facility management; 2. Committing to implement; 3.Preparing to implement through mobilisation of resources; 4.Evidence of KMC implementation; 5. Integration into routine care; 6. Sustaining KMC practices with audit data and staff development. This tool was used to objectively track changes to KMC implementation at EFSTH NNU, with data collected annually from the start of the PhD to the end of the eKMC trial (May 2020) using the West African version of the assessment tool from 2018 onwards. Using this tool, it was demonstrated that KMC was integrated into routine care during the PhD preparation phase (September 2016 – April 2018) and prior to onset of the eKMC trial, with further progress in sustaining KMC practice during the eKMC trial period (Fig.3-4).

Figure 3-4. Sustained progress in KMC implementation at EFSTH during PhD period



3.4. eKMC trial feasibility and preparation of study site

3.4.1 Feasibility study to inform eKMC trial protocol development

A prospective observational study was conducted at EFSTH NNU with the aim of understanding the target population for the subsequent eKMC trial of mild-moderately unstable neonates and to detect barriers to trial recruitment to inform development of the eKMC trial protocol.

All neonates admitted to EFSTH NNU during a three-month period (21st April – 21st July 2017) were screened for admission weight, age, and maternal availability within 24h of admission. Written informed consent was taken from caregivers of neonates <2000g and <20h to obtain socio-demographic, clinical and anthropometry (weight, head circumference, length). At this stage in the protocol development, age <20h was being considered as an entry criteria, which was later revised to <24h. Data was collected by trained MRCG research nurses and EFSTH nurses as soon as possible after admission. Clinical data included: examination and assessment for neonatal encephalopathy (NE) using Sarnat score;[82] gestational age assessment using New Ballard score with axillary temperature, blood glucose and vital signs recorded every 30 minutes for a 6-hour period. Nonin 2000A pulse oximeter was used for measurement of heart rate and oxygen saturation (SpO_2) with manual recording of respiratory rate, work of breathing and need for resuscitation. Participants were classified post-hoc as being stable, mild, moderate, or severely unstable as per the draft stability definitions and the vital signs measured during the 6h observation period. Neonates were followed up weekly during admission with telephone follow-up at 7d and 28d of age post-discharge and recording of inpatient treatments and outcome (death/discharge).

227 neonates were admitted during the 3-month observation period. 39% (89/227) of neonates weighed <2000g, of whom 75% (67/89) were aged <24h old at time of admission. Within the target trial population (<2000g and <24h old at admission), 52% (35/67) were consented and underwent clinical assessments and follow-up. The reasons for non-recruitment of neonates <2000g are detailed in Table 3-5, linked to implications for the eKMC trial and actions taken to maximise recruitment and provision of the intervention.

Despite having a small sample size, this feasibility study also provided insights into data collection methods with this vulnerable population, particularly with reference to anthropometry and gestational age assessments (Table 3-5). This informed the development of protocol and study specific procedures (SSPs) and highlighted the need for enhanced training and standardisation methods to reduce inter-observer variability. The high rates of maternal unavailability during the first 24h of admission and high twinning rates were identified as important barriers for provision of the intervention. An enhanced role for female relatives in providing KMC was identified as a potential solution to this barrier and will be explored further in Chapter 4.

Table 3-5. eKMC feasibility study key findings with implications for recruitment, data collection and provision of the intervention to unstable neonates <2000g

Feasibility study finding	Implications for eKMC trial	eKMC protocol/operational actions
Recruitment barriers for all neonates <2000g and <24h old (n=67)		
Severely unstable or died before/during assessment (21%, 14/67)[a]	High mortality rates early in admission may limit recruitment	- Sensitisation at referral health facilities to encourage timely referral and appropriate management
Mother unavailable during first 24h of admission (19%, 13/67)[a]	Mothers may not be available to provide informed consent	- Consent process to include non-parental caregivers with later parental assent
Consent declined (11%, 6/54)[a]	- Low quality consenting process may affect recruitment - Lack of community awareness about the research	-Enrolment by MRCG nurses with intensive training -Community sensitisation activities, including at antenatal clinics
Absent or busy personnel (10%, 7/67)[a]	Need adequate staffing for 24/7 for recruitment	Research personnel available 24/7 for screening & recruiting activities
Feasibility & reliability of data collection in recruited neonates <2000g (n=35)		
Stability monitoring began at median age 5.5h	Feasible to conduct stability screening within 24h of admission	Training of personnel on stability definitions with job aids and quality checks
Missing anthropometry data uncommon except for length[b]	Obtaining study-specific weights is feasible but length measurement is challenging in unstable neonates	Length measured within 48h of recruitment with standardisation assessments to detect and reduce inter-observer variability
Low quality data from Sarnat score for evaluation of NE	Formal assessment for NE is unlikely to give reliable data	Seizures taken as proxy for NE
High rates of missing gestational age data (14%, 5/35) & low nursing confidence with assessments	High likelihood of unreliable or missing gestational age estimates, with risk of inter-observer variability	New Ballard score performed by clinicians with high quality training & double blind standardised checks to reduce interobserver variability
Resuscitation required in 25% (7/28) of neonates who survived to discharge	Reliance on resuscitation as marker of severe stability may over-estimate proportion of severely unstable neonates	Stability definitions and screening process refined, with prolonged screening period of severely unstable neonates
Feasibility of providing early KMC to mild-moderately unstable neonates <2000g (n=25)		
Mothers unavailable within 24h of admission (19%, 13/67)	Mothers may not be available to provide the intervention	Female relatives are potential surrogate KMC providers
Twin pairs comprised 24% (6/25) of mild-moderately unstable neonates	High twinning rates may affect quality and quantity of intervention delivered and bias outcomes if unbalanced between arms	-Female relatives as surrogate KMC providers for twins -Adjust for twins in statistical analysis methods
Mortality of mild-moderately unstable neonates <2000g (n=25)		
28d mortality = 56% (14/25)	Choice of primary outcome as mortality is feasible if recruitment barriers addressed	392 participants required to detect 30% reduction in mortality

a) Reasons for non-recruitment also included enrolment to another MRCG study (n=1) and major congenital malformation (n=1); total reasons equal >67 due to presence of multiple factors; b) Weight measured in 35/35 (100%); head circumference in 33/35 (94%) and length in 26/35 (74%), with concerns about handling unstable neonates cited as reason for not collecting data

Abbreviations: KMC = Kangaroo Mother care; NE = Neonatal encephalopathy; MRCG = Medical Research Council Unit The Gambia at LSHTM

The 28-day mortality rate for neonates <2000g and <24h who fulfilled the proposed stability criteria as mild-moderately unstable was 56% (14/25) (Table 3-5). This data was used to inform the sample size calculation for the trial, which was estimated as total 392 neonates to detect 30% relative reduction in 28-day mortality. Based on the observed recruitment barriers and published admission rates for the site,[27] the projected number of eligible neonates <2000g (estimated 245/yr) was considered sufficient to achieve the target sample size (n=392) within a two-year recruitment period.

3.4.2 Trial site modifications to provide early KMC prior to stability

Modifications were required to the EFSTH NNU environment, inpatient flow, and infra-structure/equipment so that early KMC could be provided to unstable neonates. The changes were made in collaboration with the EFSTH senior nursing and medical team with sensitisation of EFSTH nurses and doctors.

3.4.2.1 Ensuring a safe and respectful environment for delivery of KMC prior to stability

Providing a comfortable and safe environment for KMC providers is an important enabler for KMC provision with stable newborns[51] and applies equally to unstable neonates, especially to encourage prolonged periods in KMC position. Thus, we introduced small adult sized beds, mosquito nets and pillows onto EFSTH NNU, for exclusive use by the intervention arm. Introducing beds onto the critical ward was not possible due to lack of space and HCW concerns about over-crowding and infection control implications. Initially two beds were located on the “stable ward” alongside incubators and a radiant heater for the control arm (Fig.3-5). However, during the early trial phase (May – June 2018) it became apparent that two beds were insufficient to meet recruitment targets and the neonatal unit was re-configured with the trial area moved to the former “septic ward” and provision of four beds for the intervention arm, one radiant heater and one to three incubators (Fig. 3-6). Moveable screens were available to provide privacy for KMC providers on the busy NNU, with hospital made KMC Thari wrappers available for KMC provision. Plans were made for KMC providers in the intervention arm to have access to the KMC unit washroom, but they did not have access to a separate bed on the “mothers ward” due to limited bed capacity. The mothers in the control arm were able to continue using the beds and wash facilities in the “mothers ward” as per standard care.

Figure 3-5. Delivery of the eKMC trial intervention at EFSTH neonatal unit

Source. H.Brotherton, May 2018

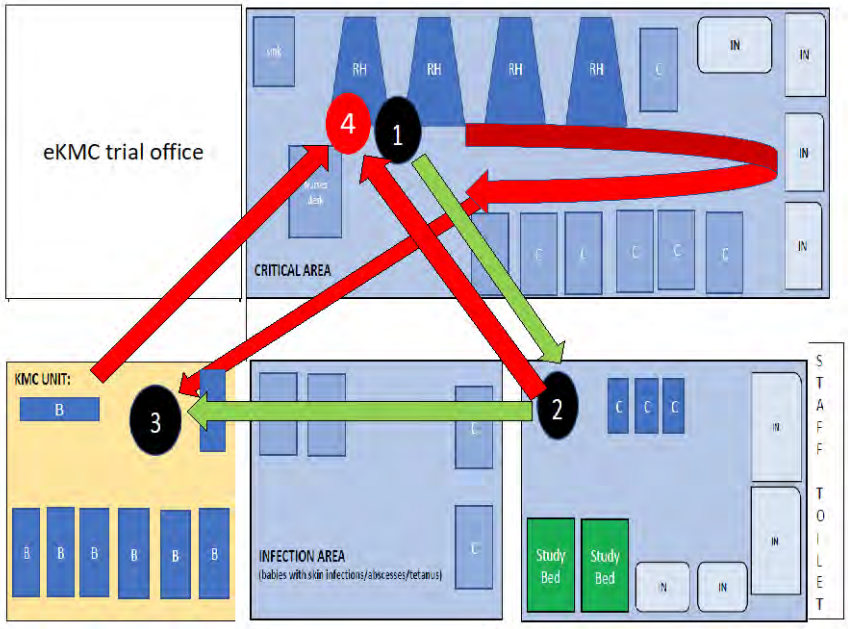
Figure 3-6. Reconfigured eKMC trial area at EFSTH neonatal unit

Source. H.Brotherton, January 2019

3.4.2.2 Re-organisation of patient flow

Due to the positioning of beds for the intervention arm, it was necessary to adjust the usual patient flow around the NNU for eKMC trial participants (Fig.3-7). Following screening and recruitment in the critical area, neonates were transferred to the trial area in the "stable ward" or latterly the infection area, to receive ongoing care and intervention or control procedures. In the event of a significant deterioration requiring resuscitation, bCPAP or more intensive monitoring, participants were transferred back to the critical area and, thereafter, followed the usual patient flow around the NNU.

Figure 3-7. eKMC trial participant flow at EFSTH neonatal unit



1) Screening & recruitment procedures performed whilst on "admission radiant heater"; 2) Transferred immediately to "trial area" for intervention/control procedures and all other care including oxygen and/or IV fluids; 3) Transferred to KMC Unit once not requiring oxygen and IV fluids, with subsequent discharge home; 4) In the event of deterioration needing resuscitation, bCPAP or closer monitoring, neonates in both arms were transferred from trial area or KMC unit to the critical area and from there followed the usual flow without returning to the trial area

3.4.2.3 Modifying NNU infra-structure

Modifications to the NNU infra-structure included installation of additional electricity sockets and wiring to enable usage of the radiant heater and equipment in the trial area. We supplied an additional oxygen concentrator for exclusive use by participants. Mosquito netting on the windows and a sink in the trial area were also repaired. Incubators and oxygen concentrators intended for participants underwent maintenance service checks by the MRCG Biomedical Department prior to trial onset.

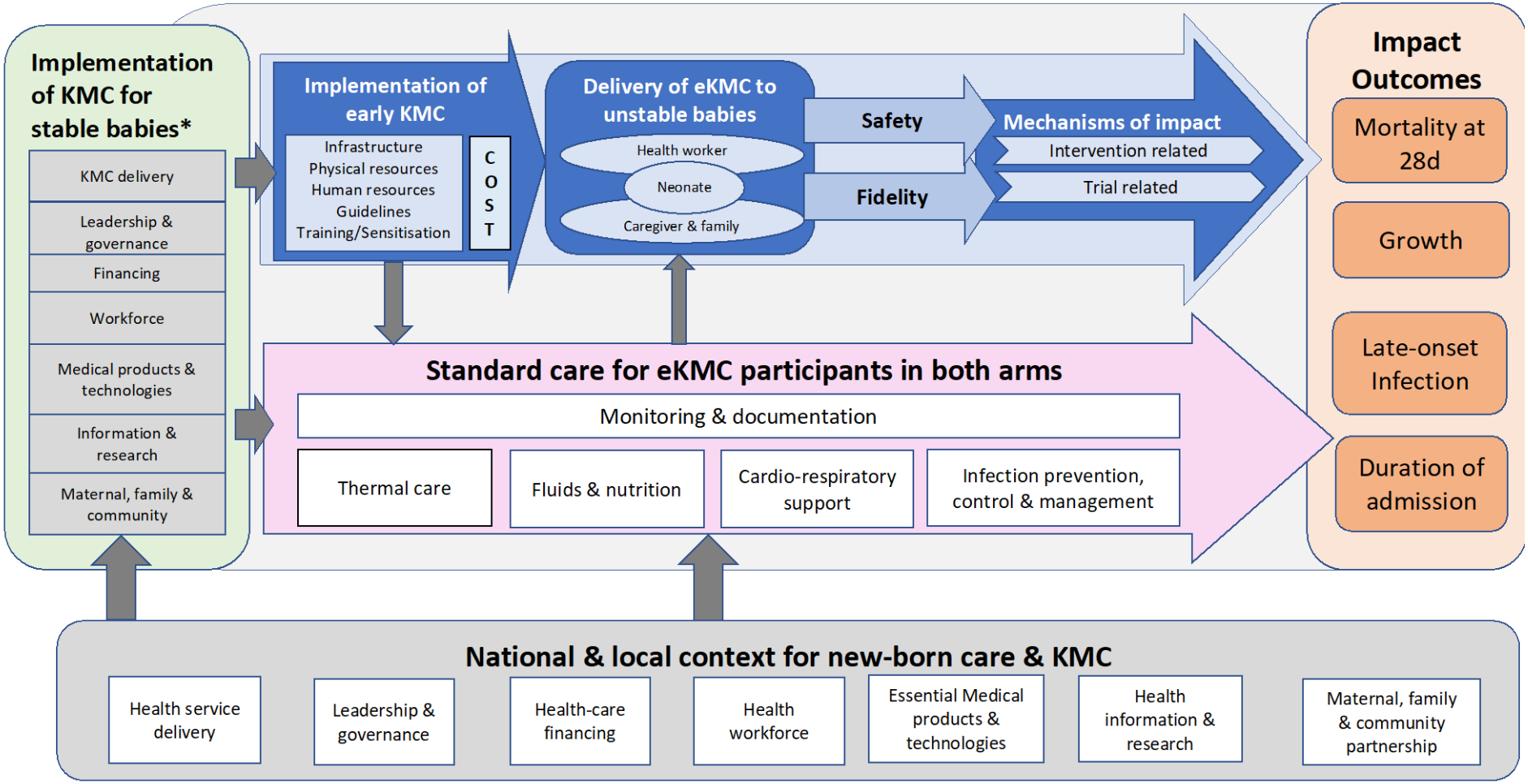
3.4.3 Internal pilot phase

An internal pilot phase was included in the eKMC trial protocol with the aim of piloting data collection tools and study specific procedures (SSPs), including intervention provision. The first 10 recruited participants were included in this piloting phase and, as they met eKMC protocol eligibility criteria and were protocol compliant, were included in the main trial analysis. Important insights gained from this piloting phase included challenges to intervention delivery, especially to unstable twins, and in combination with safe IV fluid administration. SSPs were adapted to facilitate safe intervention delivery with training of eKMC research team and EFSTH nursing/medical personnel on avoiding obstruction of IV drip lines, checking flow rates and siting of cannulas in newborns hands (instead of feet) where possible. The limited number of trial beds for KMC providers was also identified as a major recruitment barrier during this phase. The initial data management plan specified combined paper/electronic case report forms (CRFs), which was found to be unfeasible during the internal pilot phase and the database was adjusted to enable electronic data capture only.

3.4.4 Development of a conceptual framework to guide process and implementation data collection

Process evaluations are recommended as an essential component of clinical trials of complex interventions[83] and are important in intervention development and testing, to clarify causal mechanisms and identify contextual factors associated with variations in outcome. MRC have published guidance on developing and evaluating complex interventions, with a framework of four phases (development; feasibility/piloting; evaluation and implementation) and the relationships among them.[50] During the preparation phase I developed a conceptual framework (Fig.3-8) based on the MRC framework, to guide collection of process and implementation data to understand 1) How changes to standard care may impact on trial outcomes and 2) How to implement and deliver early KMC to unstable neonates. Although conduct of a comprehensive process evaluation was beyond the scope of this PhD, this framework helped to inform collection of process data, which will be considered in Chapter 7 (pathways to mortality and mechanisms of early KMC).

Figure 3-8. Conceptual framework to guide collection of process and implementation data during the eKMC trial



**Vesel et al, 2015[62]*

3.5. Summary of preparations for trial implementation

Extensive activities were undertaken at the eKMC trial site in preparation for the eKMC trial, principally to introduce KMC as standard care and to provide standardised, internationally recommended care to both trial groups. The environmental surveillance activities identified clinically relevant and widespread presence of MDR and highly pathogenic GNB prior to eKMC trial onset, indicating the high risk of nosocomial infection at the site. The feasibility study was useful to evaluate recruitment barriers and to gain insights into the target population of mild-moderately unstable neonates, especially for assessment of 28-day mortality, the intended trial primary outcome. These insights enabled design of the trial protocol based on local data and were complemented by an internal pilot period which helped to refine trial procedures and data collection tools. Further modifications and reconfigurations at the trial site were necessary for implementation of early KMC prior to stability, with consideration of providing a safe and respectful environment for KMC providers, safe patient flow around the NNU and infrastructure/equipment changes to ensure safe KMC provision alongside other required SSNC treatments. In recognition of the potential impact of these changes on trial outcomes, a conceptual framework was developed to guide collection of process data, as well as to inform assessment of intervention delivery, fidelity and safety.

Chapter 4 - Perceptions of female relatives towards small and sick newborn care and kangaroo mother care (Article 1)

4.1. Scope of the chapter

Chapter 4 presents the first research paper entitled ""We all join hands": Perceptions of the Kangaroo Method amongst female relatives of newborns in The Gambia". This paper provides an in-depth understanding of the perceptions of Gambian female relatives towards SSNC and KMC. A specific aim was to explore the acceptability of female relatives as surrogate KMC providers, to enable implementation of early KMC during the eKMC trial. The paper also provides understanding of contemporary Gambian women's attitudes to SSNC and barriers/enablers for KMC provision from the perspective of a previously understudied population.

4.2. List of figures

4.3. List of tables

4.4. Supplementary material

The supplementary material, as detailed in the published article, includes the in-depth interview guide (Annex A-4-1) and KMC information sheet (Annex A-4-2) which were used during interviews. The work was reported in accordance with Standards for Reporting Qualitative Research (SRQR) (SRQR checklist, Annex A-4-3).

4.5. Citation

Brotherton H, Daly M, Johm P, Jarju B, Schellenberg J, Penn-Kekana L, Lawn JE. **"We all join hands": Perceptions of the kangaroo method among female relatives of newborns in The Gambia.** Qualitative Health Research 2021; 31(4): 665-676. Doi: 10.1177/1049732320976365

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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	1601409	**Title**	Dr
First Name(s)	Helen		
Surname/Family Name	Brotherton		
Thesis Title	Early Kangaroo Mother Care for mild-moderately unstable neonates <2000g in The Gambia		
Primary Supervisor	Joy Lawn		

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?	Qualitative Health Research as: Brotherton H, Daly M, Johm P, Jarju B, Schellenberg J, Penn-Kekana L and Lawn JE. "We All Join Hands": Perceptions of the Kangaroo Method Among Female Relatives of Newborns in The Gambia. Qual Health Res 2021;31(4):665-676. DOI: 10.1177/1049732320976365		
When was the work published?	December 8, 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**

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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 conceived of the research idea and designed the study and interview guide in collaboration with the co-first author (Maura Daly, MsC student at LSHTM), who was supervised by myself as lead supervisor and Prof J. Schellenberg as co-supervisor. I supervised Maura Daly and Bintou Jarju during data collection at the site, giving input to refinement of the interview guide. I had previously trained Bintou Jarju in qualitative data collection methods. Along with Loveday Penn-Kekana, I gave oversight to the analysis process and interpretation of data. Along with Prof Schellenberg I reviewed the work as presented in the MSc thesis prepared by Maura Daly. I led the adaptation of the MSc thesis to prepare it as a manuscript for publication, adding important intellectual interpretations, such as relation to kinship theories. Joy Lawn and I developed an explicit conceptual framework from our implicit assumptions. I led all subsequent revisions of the manuscript, with consideration of comments from co-authors and peer-reviewers.

SECTION E

Student Signature	Helen Brotherton
Date	30th June 2021

Supervisor Signature	Joy Lawn
Date	6th July 2021

Research Article

"We All Join Hands": Perceptions of the Kangaroo Method Among Female Relatives of Newborns in The Gambia

Qualitative Health Research
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Abstract

Family support is essential for kangaroo mother care (KMC), but there is limited research regarding perceptions of female relatives, and none published from West African contexts. In-depth interviews were conducted from July to August 2017 with a purposive sample of 11 female relatives of preterm neonates admitted to The Gambia's referral hospital. Data were coded in NVivo 11, and thematic analysis was conducted applying an inductive framework. Female relatives were willing to support mothers by providing KMC and assisting with domestic chores and agricultural labor. Three themes were identified: (a) collective family responsibility for newborn care, with elder relatives being key decision makers, (b) balance between maintaining traditional practices and acceptance of KMC as a medical innovation, and (c) gendered expectations of women's responsibilities postnatally. Female relatives are influential stakeholders and could play important roles in KMC programs, encourage community ownership, and contribute to improved outcomes for vulnerable newborns.

Keywords

neonate; newborn, preterm; low birth weight; kangaroo mother care; skin-to-skin; family; grandmother; female relative; gender; qualitative; in-depth interviews; The Gambia; West Africa

Background

Every year, nearly 15 million newborns are born preterm (<37 weeks of gestation; Blencowe et al., 2012) closely linked with 20 million born with a low birth weight (LBW; birth weight <2,500 g; Blencowe et al., 2019). The majority of these vulnerable newborns are born in South-East Asia and sub-Saharan Africa (Ashorn et al., 2020). The smallest and most preterm newborns have the highest risk of illness and death during the first month after birth (Lawn et al., 2014) with complications of prematurity now being the most common direct cause of death in childhood (United Nations Inter-Agency Group for Child Mortality Estimation [UNIGME], 2020). Despite the high risk of preterm or LBW birth, in Africa there is a critical gap in hospital care of small and sick newborns which must be addressed if newborn and child survival targets, now included in the Sustainable Development Goals, are to be met by 2030 (World Health Organization [WHO], 2020).

Kangaroo mother care (KMC) is a package of care provided by caregivers, mostly the mother, in which small newborns receive prolonged skin-to-skin contact (Vesel et al., 2015) in the "kangaroo position." KMC provides warmth, promotes exclusive breast milk feeding and weight gain, and reduces the risk of infections, often resulting in shorter hospital stay (Conde-Agudelo & Diaz-Rossello, 2016). KMC is recommended as standard care for all stable newborns (birth weight ≤2,000 g; WHO, 2015b) and has the potential to save an estimated 450,000 newborn lives per year (Bhutta et al., 2014) given a 40% mortality reduction with KMC compared to incubator care (Conde-Agudelo & Diaz-Rossello, 2016). Being in the kangaroo position also reduces stress for both KMC

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provider and newborn, helps manage neonatal pain (Gibbins et al., 2015) and promotes bonding and positive parental mental health (Mörelius et al., 2015). Long-term benefits of KMC have also been reported with decreased hyperactivity and less school absenteeism (Charpak et al., 2017), indicating positive lifelong effects for small newborns after KMC.

Despite first descriptions in Colombia four decades ago (Ray-Sanabria & Martinez-Gomez, 1986) and strong evidence of benefit (Conde-Agudelo & Diaz-Rossello, 2016), the global coverage of KMC is generally low (Vesel et al., 2015). Being in the kangaroo position for 20 hours per day (continuous KMC) is recommended for maximum mortality effect (Conde-Agudelo & Diaz-Rossello, 2016). However, continuous KMC is a major commitment for women and more challenging if they are ill, recovering from cesarean sections or had multiple births. Hence, family support to enable provision of continuous KMC is key (Mazumder et al., 2018). Yet, KMC adoption in resource-limited settings, including Africa, is impeded by lack of family support to enable (a) provision of KMC, especially continuously and (b) undertaking other domestic or family responsibilities (Seidman et al., 2015). Post-discharge continuation of KMC with regular hospital follow-up is an essential part of KMC and also requires buy-in and considerable support from the family and community. Understanding family perceptions toward KMC is also important for community ownership, a key health system bottleneck for KMC implementation (Vesel et al., 2015).

There is limited published data regarding perceptions of family members toward KMC (Kambarami et al., 2002; Seidman et al., 2015; Smith et al., 2017), particularly for grandmothers and other female relatives who play a central advisory role to mothers on newborn care practices (MacDonald et al., 2020; O'Neill et al., 2017). We found no published research on this topic specifically from West African contexts.

The purpose of this study was to understand the perceptions of female relatives toward KMC in a resource-limited setting in which KMC had not yet been implemented. A specific objective was to explore the feasibility and acceptability of female relatives acting as substitute or surrogate KMC providers for small, vulnerable newborns.

We were guided by a conceptual framework which proposes that KMC implementation can be considered at three levels: (a) mothers, fathers, and families; (b) health-care workers; and (c) facilities (Chan et al., 2016). We further developed and refined this framework to examine the layers of interpersonal and intrasocietal influences on the key stakeholders involved in KMC implementation (Figure 1). Using this conceptual framework, we considered the perspectives of female relatives within the context of the other layers of the model, especially the mothers, and sought to identify barriers and enablers to adoption of KMC from their perspective and within their own systems of adaption, cultural norms, and means of access.

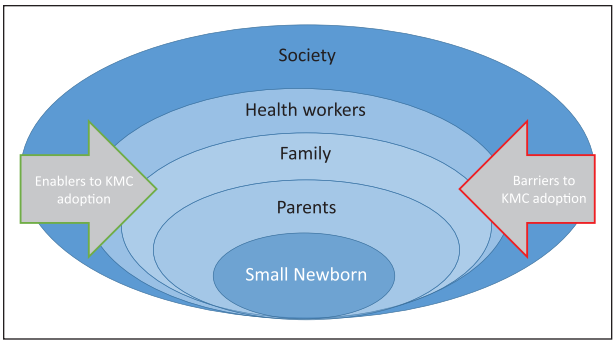

Figure 1. Conceptual framework for implementation of kangaroo mother care (KMC), considering the layers of key stakeholders.

Method

Based on the concept that perceptions of newborns and their care are influenced by social phenomena, we aimed to construct accounts of participants' experience, which were collected using in-depth interviews, observations, and reflexive field notes. The study formed part of the formative phase for a randomized controlled trial investigating KMC before stabilization in neonates weighing <2,000 g (Brotherton et al., 2020).

Political Economy and Household Structure in The Gambia

The Gambia is the smallest country on mainland Africa, with the fourth highest population density and population of ~2.08 million in 2017 (The Gambia Bureau of Statistics, 2019). The predominant religion is Islam (90%), and the Mandinka are the largest ethnic group (35%) followed by Fula (25%), Wolof (15%), and Jola (10%; The Gambia Bureau of Statistics and ICF International, 2014). Polygamy is commonplace, and the most common household structure for all ethnic groups is patrilineal, multigenerational, and extended family groups residing within a compound of varying size, depending on the domestic cycle (Kea, 2013). Compounds typically include a husband, his wives, his married sons, and their wives and children, any unmarried children, widows or divorced sisters, and other extended family (Kea, 2013; Sear et al., 2002).

Neonatal Morbidity and Mortality in The Gambia

The neonatal mortality rate in The Gambia reduced from 49/1,000 live births in 1990 to 26/1,000 live births in 2018 (UNIGME, 2019). Approximately 17% of Gambian neonates were born LBW in 2015 (UNIGME, 2019) and 12% born preterm (Chawanpaiboon et al., 2019), with complications of prematurity the second most common cause of neonatal death at the neonatal referral hospital (Okomo et al., 2015).

Hospital Setting

The study took place at the Edward Francis Small Teaching Hospital (EFSTH) neonatal unit, the national neonatal referral unit and the only teaching hospital in The Gambia. Newborns were admitted to the study site from the EFSTH maternity unit (approximately 7,000 births per year) or from other hospitals or home with two thirds of admissions born outside EFSTH (Okomo et al., 2015). At the time of this study in 2017, KMC was not practiced at EFSTH nor widely in The Gambia (Ekholuenetale et al., 2020), although mothers were advised to provide skin-to-skin contact for 30 minutes immediately after feeding for clinically stable, small newborns. Small or sick newborns were cared for under radiant heaters or incubators, often with multiple occupancy, and with few nurses.

Sampling

Eligible participants were adult (>18 years) female relatives of newborns weighing ≤2,000 g who were admitted to the study site between April and July 2017. We used purposive sampling to identify participants by approaching mothers of currently hospitalized neonates or those discharged within the preceding month. They were contacted by the interviewers in person or by phone, and invitations were extended to their female relatives. Women who were willing to participate contacted the interviewers to arrange a convenient time, and transport expenses were provided. Because different generations and family lines may have different perspectives, we aimed to include maternal and paternal relatives from a range of generations. All participants interviewed were from different families and represented a different neonate. Sample size was based on the availability of participants within the study period.

Data Collection

Semi-structured interviews were conducted over a 5-week period from July to August 2017 by the interviewers: a non-Gambian female midwife researcher and a multilingual Gambian female field worker. The Gambian interviewer enhanced the credibility of the interviewing team and was able to elucidate and interpret participants' comments within the cultural context in which they were intended (Guba & Lincoln, 2005). Neither interviewer was involved in the clinical care of the participants or their newborn relatives.

A semi-structured interview guide was used with open-ended questions concerning knowledge and perceptions of newborns, care of small newborns, and KMC (Supplementary File I). Written informed consent, including for audio-recording, was obtained in the participants' preferred language, with impartial witnesses present for illiterate participants. Informed consent documents were in English, with verbal translation to local languages during the consent process, as per standard local consenting practice in view of the most common local languages having no formal written standard in routine use. Interviews were then conducted in Wolof or Mandinka, as preferred by the participant, in a private, nonclinical room at the hospital. A pictorial information sheet was used to assist the discussion (Supplementary File II). The interviews lasted between 30 and 40 minutes (average 37 minutes) and were recorded on an ICDPX 440 Sony digital recorder. The interviews were conducted by the same interviewers with the Gambian interviewer leading the interview and the non-Gambian interviewer present for observation of the interview process and reflexivity. The interviewers worked closely together to ensure understanding of the interview guide, and both were experienced in conducting interviews, including on similar topics. The interviewers were aware that as interviews were conducted in the hospital, participants possibly associated the study with the hospital and despite assurances of confidentiality and independence, this may have led to participants sharing what they thought the interviewers wanted to hear. To try and address this, we attempted to build rapport using a warmup session, and the semi-structured interview style allowed participants to lead portions of the interview. As only one interviewer conducted interviews, we were confident that internal validity of the questions was maintained between sessions.

A pilot of two interviews was used to refine the interview guide and to ensure that the Gambian interviewer was familiar with the guide and able to readily translate into the spoken language. After each interview, the interviewers debriefed, which helped maintain reflexivity, improved interview technique, and challenged established assumptions during the analysis and writing. A field diary was kept to document the context and reflections from the interviews, informal conversations with hospital staff and insights into potential findings. Interviews were translated and transcribed into written

English text by the same interviewers to ensure consistency and dependability (Tuckett, 2005). Three randomly selected transcripts underwent validation by an independent research nurse fluent in the local languages and English to monitor for accuracy of translation, and no major discrepancies were identified. The use of these research strategies contributed to the rigor of the data collection, especially the reliability and internal validity of data collected (Guba & Lincoln, 2005).

All participants' data were pseudonymized from the time of enrollment with unique study identification codes for confidentiality. All recordings were deleted from the recorder after transcription. Recordings and transcripts were securely stored on an access-restricted, central server at London School of Hygiene & Tropical Medicine (LSHTM). Ethical approval was obtained from the ethics committees at LSHTM (Ref. 12398) and The Gambia Government/Medical Research Council Joint Ethics Committee (Ref. 1535).

Analysis

Thematic analysis was conducted using an inductive framework (Braun & Clarke, 2006), allowing codes and themes to develop directly from the data. Due to time constraints, the full transcripts were read and coded by one researcher (the non-Gambian midwife interviewer), who then worked in a cell of qualitative researchers to map, reflect, and refine codes and interpretations of themes. This process was used to help strengthen the reliability of the coding (Guba & Lincoln, 2005). Transcripts were read twice with line-by-line coding on the third reading using NVivo 11 qualitative data analysis software (QSR International Pty Ltd.). The fourth reading focused on merging and reorganizing codes and examining unexpected findings and discrepancies. Codes were then collated into themes, which were refined through iterative analysis and thematic mapping. Themes evolved both directly from the data on a semantic level from explicit meanings and a latent level from interpretation of underlying patterns and ideas (Braun & Clarke, 2006). Quotes were selected to reflect the refined themes. This article was prepared in consultation with Standards for Reporting Qualitative Research (O'Brien et al., 2014).

Results

Participant Characteristics

In total, 11 women, representing three generations of maternal and paternal family lines, were interviewed. The relatives consisted of seven grandmothers or great-grandmothers (both paternal and maternal) and four aunts (all maternal). Two women had no children of their own, and the other nine participants had a mean parity of 6.6 ($SD = 2.1$). The predominant ethnic representation was Mandinka (7/11, 64%), and all participants were practicing Muslims. All participants, except one, were resident in a rural region at time of interview. Only two women had attended secondary school, with the remainder receiving only primary level (3/11, 27%) or no formal education (6/11, 55%). All women worked in manual or informal employment, such as market traders, subsistence farmers, or housewives. Most (10 of 11) participants were related to a current in-patient and one to a recently discharged newborn.

Themes and Perceptions

Three interlinked themes were identified, which gave insight into both contemporary attitudes to newborn care in The Gambia and the acceptability and feasibility of Gambian female relatives supporting KMC. Barriers and enablers for KMC provision and support by female relatives were identified for each theme (Table 1).

Theme 1: Collective family responsibility for newborn care practices, including KMC. Participants identified themselves as part of a larger collaborative unit with a unified, shared responsibility for newborn care. This collective identity was reflected in the cooperative processes of cooking, farming, and health decisions occurring within a compound in which the extended family reside. Participants identified their family as a single unit, with a shared responsibility for the maintenance of the family's well-being and prosperity:

> Myself, my husband and my co-wife and my co-wife's elder son. We all join hands to care for our children. We are all united. (Maternal grandmother, market trader, Parity 8)

Although all members of the family were considered essential parts of the family unit, participants outlined gendered divisions of responsibility and a general deference to the authority of elder family members in most matters, including knowledge and inheritance of skills. With regard to newborn and maternal health decision-making, this authority was the domain of female relatives, with a hierarchy based on increasing age and elder females holding substantial influence for the care of mothers and their babies. The paternal grandmother of the baby was regarded as the most respected authority for advice on postnatal care and participants deferred to her as the senior authority. This hierarchy has a practical flexibility, and in the absence of the paternal grandmother, other female relatives assume the role, particularly the maternal grandmother followed by co-wives (other wives of the grandfather) or maternal aunts:

Table 1. Barriers and Enablers for Adoption of KMC, as Perceived by Female Relatives of Newborns in The Gambia.

Theme	Barriers to KMC Adoption	Enablers of KMC Adoption
1. Collective family responsibility for newborn care practices, including KMC	- Lack of buy-in and acceptance by female elders. - Fathers too busy to be involved and may not understand the importance of KMC.	- Newborn care is a shared responsibility for all female relatives. - Elder female relatives are key decision makers for newborn care. - Flexibility within the extended family can support the mother ("step-in" roles). - Helping mothers with KMC is a reinforcement for positive family relationships.
2. Evolving traditions and the role of medical innovation in acceptance of KMC	- KMC is viewed as being different to traditional newborn care practices. - KMC (carrying baby on front) is viewed as a Western practice. - Uninformed & negative community perceptions of KMC may prevent adoption.	- Small newborns are exempt from traditional newborn practices. - The KMC wrapper protects small newborns from exposure to evil spirits or "foul wind." - KMC is viewed as a prescribed treatment not a traditional practice. - Respect for medical authority
3. Societal expectations of women's roles and responsibilities in the postnatal period	- The physical requirements of KMC will interfere with the ability to perform domestic duties. - Women will be unable to do farming work at the same time as KMC. - KMC is an additional obligation for the female relative, who has her own domestic & labor responsibilities.	- KMC is part of women's responsibility to protect the newborn from harm. - Female relatives have a responsibility to support mothers, which extends to KMC and domestic chores. - Intra-household task sharing allows for shifting of domestic responsibilities between women. - Female elders can use their authority to task-shift within the compound or family.

Note. KMC = kangaroo mother care.

> That is the role of her mother-in-law, or her own mother or father-in-law and sisters-in-law. They should help the new mother, but if the mother-in-law is less busy, she should be the right person to help. (Paternal grandmother, farmer, Parity 8)

> Mothers-in-law should come to support their daughters-in-law, but for our case my granddaughter's mother-in-law is not there. That is why I am here to support her. (Great grandmother, farmer, Parity 7)

Senior family members took pride and ownership in their role as care providers and were eager to engage in any form of newborn care:

> If I wasn't here [in hospital], things would not work well. I was the one giving care to the baby. (Maternal grandmother, farmer, Parity 10)

Elder female relatives had learned newborn care practices from their own elders, and it was perceived as their responsibility to maintain this system of knowledge inheritance. The authority was explained by seniority of experience accumulated in caring for their own children and other mothers, and they described mothers and newborns as being "under the care" or "the responsibility of" the mother-in-law:

> That is the role of we, the eldest, that is our responsibility. We need to advise them, because they don't have experience on caring for a baby. (Maternal grandmother, farmer, Parity 5)

The physical structure of the compound was described as a hub of family life and a geographical determination of unity, authority, and responsibility. When a new mother returned to the compound of her in-law relatives, she was placed under the umbrella of their advice and protection, and her own mother assumed that role if she returned to her parents' compound. Nearly all participants expressed the importance of the wider family and community acceptance of KMC, indicating that until others around them in the community were aware of the benefits, KMC would not be encouraged.

Female relatives on both maternal and paternal sides expressed satisfaction and a sense of empowerment after learning about KMC during the interview. They viewed their own and other female relatives' participation in KMC as a fulfillment of their obligations to their relatives and a validation of their position as an authority on newborns:

> Grandmothers will feel happy about it, the same thing applies to great grandmothers, they will say that they have taken care of their children and their children's children. I'm

> sure they will be happy about it. (Maternal grandmother, farmer, Parity 10)

Overwhelmingly, the participants agreed in principle to provide KMC themselves in the absence of the mother, whether they viewed the task to be difficult or easy, because of their identified sense of duty to family health:

> I will say yes and I will be willing to do it, because I know it is good for the baby. (Maternal grandmother, farmer, Parity 5)

> I will say yes, because the baby is my grandchild, I will help my daughter to give kangaroo care to the baby. (Maternal grandmother, farmer, Parity 10)

In addition, their potential contributions to KMC were described as a salve or reinforcement to intra-household relations:

> Our relationship would be good, because if you help your relative to do it [KMC] she will know that you like her and her baby. (Maternal aunt, cook, Parity 6)

The provision of KMC was predominantly seen as being within the domain of the mother and the female relatives. Participants' had mixed views towards the involvement of fathers or male relatives in KMC. Men were deemed as being too busy to participate, or that KMC was something a man would have to do in private, away from the gaze of neighbors.

Theme 2: Evolving traditions and the role of medical innovation in acceptance of KMC. An important theme that emerged was the balance between maintaining tradition and embracing new practices, such as KMC, which was viewed as a medical innovation. Female relatives expressed a sense of value and honor in maintaining traditional methods of caring for mothers and newborns, especially traditions involving the extended family structures and seasonal agricultural lifestyles:

> In our culture, I mean we the Mandinka, if a woman gives birth if there is an elderly person in the compound, [the elderly person] will be responsible to bathe the baby for one week after birth, after the naming ceremony the in-law or mother to the new mother can take over from the elderly person. (Paternal grandmother, farmer, Parity 7)

However, participants also discussed that some traditions were changing or were no longer valuable, with identification of practices that had changed for the better, such as the use of disposable diapers, provision of antenatal care, and avoidance of traditional medicine, all of which had improved the lives of mothers:

> Yes, there is a difference they make good use of the herbs, and God help them to recovery, but now we have health centre everywhere where people go for treatment, during the time of my mother's they didn't go for antenatal check-ups. (Paternal grandmother, farmer, Parity 7)

Although most agreed that newborn care practices had changed since the time of their grandmothers' pregnancies, participants expressed a hesitancy to embrace practices they sensed might affect traditions that were valued, and they articulated concern regarding the perception of their community:

> Maybe sometimes they [community/neighbors] will feel like carrying the baby in this position is not good . . . but I think they should know the importance of kangaroo care. (Maternal aunt, cook, Parity 6)

Traditions regarding care of small newborns. Small newborns, described as "babies not yet due" regardless of gestational age, were seen as particularly vulnerable to illness, both those transmitted through biomedical and supernatural means. Small newborns were also referred to as "water babies" and were considered not to be fully formed humans, leading to high risk of illness and death from supernatural means such as wind (bad air) or *Jinne* (evil spirits). It was believed that using physical barriers, such as fabric to wrap or swaddle a baby, protects small newborns from such supernatural forces:

> I heard it from the elders, that they [small newborns] should not be exposed to the public, if exposed they become sick easily and pass away. (Maternal aunt, market trader, Parity 0)

> A baby should be wrapped to protect her from evil eyes, they [small newborns] are called water babies, the moment the eyes are set on them they pass away. (Maternal aunt, market trader, Parity 0)

Despite the prevalence of preterm and LBW babies born in The Gambia, none of the participants reported caring for or seeing a small newborn prior to the current admission, and many noted that a vulnerable, small newborn should be hidden from the community.

Care of the small newborn was viewed differently from usual newborn care, and therefore was flexible to the many requirements of traditional newborn care practices:

> I think babies not yet due should be wiped with a clean cloth, and they should be wrapped with heavy wrappers [fabric]. When it comes to feeding some of them cannot suck breast, I think they should be spoon-fed. (Maternal grandmother, farmer, Parity 5)

Wrapping the newborn in numerous pieces of fabric was seen as routine for all newborns but emphasized for small newborns as a means to defend against air and subsequent illness:

> Babies not yet due should not be bathed, their body should be wiped, too much water is not good for them, they need to be wrapped [in fabric] and should not be exposed to the air . . . Mothers need to be very careful of their babies not yet due. (Great grandmother, farmer, Parity 7)

There was knowledge and understanding of the higher risks of mortality associated with being born small, with some participants associating the likelihood of survival with religious beliefs:

> At the moment I am praising God at all times, because God gave it [the baby] to us. That's what I have in my mind, but I really thank God, I am praying . . . for them to survive. (Maternal grandmother, farmer, Parity 5)

Acceptability of KMC. Participants frequently commented that KMC was a Western practice, in reference to front baby carriers popular in Western countries. This contrasts with the traditional Gambian method of swaddling babies in fabric and holding them in arms for the first month after birth, after which they are carried on the caregiver's back. Female relatives voiced apprehension that they would be viewed as abandoning tradition:

> Yes, I see the white people carrying their baby this way. I first saw it with the white people . . . Well, if I don't know it, I will think they are copying the white people. Because, we know of the white people carrying their baby in front, we carry our babies on our back. (Great grandmother, farmer, Parity 7)

> You know I have seen it, but if the [other mothers] didn't see the image [KMC information sheet] they might not know that the baby is born before its time, they may think the mother is copying the western culture. (Paternal grandmother, housewife, Parity 6)

Carrying newborns on the back was viewed both as a convenience and a way by which to protect the child from harm, as the mother is physically in front of the baby. Concerns were expressed about the vulnerability of the newborns position between the mother's breasts, with a perception that the newborn was more vulnerable to harm in the KMC position:

> If you carry the baby in the kangaroo position, you need to be careful not to fall down. (Paternal grandmother, farmer, Parity 8)

> It is safer when you carry the baby on your back and tie the wrapper [fabric] properly, nothing will happen to the baby. (Paternal grandmother, farmer, Parity 7)

Despite the differences with traditional practices and reservations about safety, there was acceptance of KMC and a willingness to provide KMC themselves because it was seen as a care practice specifically for small newborns, rather than an attempt to alter traditional practices. The authority of health workers in recommending KMC was also identified as promoting KMC acceptance:

> They will accept it if it is the advice given by doctors. No, that [KMC] will not be a problem at home, it has nothing to do with traditions, if you are asked why, you will let them know it is the advice given to you by doctors for babies not yet due. (Great grandmother, farmer, Parity 7)

Overwhelmingly, innovative changes to practices such as KMC were seen as helpful and a positive change both for the participants and their families:

> I think they should like it [KMC]. I don't think it should have to be with tradition, people don't care for tradition that much now. The health of the baby is the most important thing. (Paternal grandmother, farmer, Parity 8)

In addition, participants identified similarities between KMC and traditional newborn care practices, especially the importance of keeping babies warm and protecting them from exposure to air. Many participants embraced the idea that KMC could include an outer cloth around the back of the baby and accepted this as a protective practice, similar to how newborns are traditionally wrapped in fabric.

Theme 3: Societal expectations of women's roles and responsibilities in the postnatal period. The acceptability and feasibility of KMC was rationalized through the lens of how it would influence or disrupt the expected roles and responsibilities of women (mothers and female relatives) during the postnatal period. It was acknowledged that women's responsibilities change with advancing age, with core responsibilities including obligations to family, God, housework, and, for some, farming.

Responsibility to protect the newborn. Mothers are exempt from many physical duties during the first 40 days following delivery but are expected to be the primary carer for their newborn, with the support of elder female relatives. The mother's foremost responsibility was the protection of her child, expressed through shielding the newborn from causes of illness, both biomedical and supernatural. Acts such as wrapping, keeping the baby under a mosquito net, and carrying the baby on her back were all described as physical barriers meant to protect the newborn. The physicality of KMC was identified as a potential challenge, but KMC was viewed as another method of protecting the newborn and fulfilling their responsibilities:

> It [KMC] is good for the baby . . . because when you carry your baby in front, you will be able to notice her at all times. (Maternal aunt, cook, Parity 6)

Maintaining good hygiene was also highly valued as a ritual and responsibility to ensure health for the newborn:

> The mother needs to be clean always so that the baby will be healthy. If the baby is not healthy, her mother will not be free. (Paternal grandmother, farmer, Parity 8)

> Person doing kangaroo care should put on clean cloths [fabric used to secure baby in KMC position], and pay attention to the baby, the cloths should be clean always. (Paternal grandmother, housewife, Parity 6)

Domestic responsibilities and KMC provision. Domestic duties were the central responsibility for women of reproductive age, and this was observed as a barrier to providing KMC after hospital discharge:

> She should always be careful when she is doing household work, and she should know the type of household work she can do during kangaroo care. (Maternal grandmother, farmer, Parity 5)

There was an understanding that some domestic duties were still possible in combination with KMC and that appropriate education for the mother and relatives would be helpful:

> During kangaroo care you will be able to walk around the compound, this is just like carrying the baby on your back, although you cannot bend down, but you will be able to do certain work . . . during kangaroo care you cannot cook with the baby, or bend down with the baby, you cannot pound [grain]. (Great grandmother, farmer, Parity 7)

KMC was perceived as an additional obligation for the female relative who supports the mother. However, participants were willing to modify some of their own responsibilities to accommodate the needs of the mother and newborn.

Farming obligations and support of female relatives. Many participants had strong obligations to farming, and any theoretical contributions to providing KMC were linked to the agricultural calendar. Participants described some flexibility within the household dynamics which would allow for a negotiation of labor contributions. Female elders suggested that they could use their authority to modify the expected labor and domestic contributions of KMC practicing mothers and task-shift (ask other family members to do the mother's domestic responsibilities) with other family or household members. There was a willingness and a flexibility from female relatives to provide KMC when they weren't farming:

> We can give kangaroo care before going to the farm in the morning, or we can give kangaroo in the afternoon, when we come back. (Maternal grandmother, farmer, Parity 10)

KMC was viewed as being consistent with the expected societal roles and responsibilities during the postnatal period and was viewed as feasible within both hospital and community settings.

Discussion

This in-depth, qualitative study of female relatives' perceptions of newborn care and KMC is consistent with recent calls from the WHO to conduct formative research from a family-systems perspective to improve maternal and newborn implementation programs (WHO, 2015a) and address evidence gaps relevant to implementation of high impact care (Smith et al., 2017).

We identified overarching themes of (a) collective family responsibility, (b) evolving traditions and the role of medical innovation, and (c) societal expectations of women during the postnatal period, which provide important insights into the barriers and enablers for adoption and support of KMC by female relatives (Table 1). These themes are consistent with many of those previously identified as being important for KMC adoption in previous systematic reviews of the topic, especially KMC provider buy-in and bonding, social support, and cultural context (Chan et al., 2016; Smith et al., 2017).

Historically, child health interventions have focused on the mother–child relationship without consideration of the social structures and cultural systems that influence health beliefs and behaviors (Aubel, 2014). By considering the views of family members within the context of the other layers of KMC implementation (Figure 1), we appreciate how kinship bonds among women are central to KMC practice and acceptance.

We identified an overwhelming acceptance and willingness for female relatives to support mothers, both by providing KMC themselves and assisting the mother with domestic and labor responsibilities. Shared familial responsibility, intergenerational relationships, and deference to elder female authority were key enablers for newborn care and KMC provision. The finding that women were motivated to help their relatives in an effort to reinforce intra-household relationships is consistent with the theory that kin relationships can develop through everyday experiences within the domestic sphere (Carsten, 2000).

Our finding that elder female relatives are influential for newborn care is well described in many African contexts (Aubel et al., 2004; Iganus et al., 2015; MacDonald et al., 2020) and highlights these women as key actors for the uptake and continuation of public health interventions such as KMC (Gupta et al., 2015; Iganus et al., 2015;

Mazumder et al., 2018). Programs that utilize both the decision-making influence and caretaking role of elder family members have the potential to change behavior more effectively (Iganus et al., 2015). This is in-keeping with The Every Newborn Action Plan, which advocates to incorporate influential family members, such as grandmothers, to strengthen support networks for newborn care (WHO, United Nations Children's Fund [UNICEF], 2014).

The acceptance of KMC by female relatives is balanced between respecting traditional beliefs and viewing KMC as a prescribed treatment or medical innovation for small newborns. This is linked to an observed respect for the authority of health workers. When considered through the lens of our conceptual framework (Figure 1), the wider social hierarchy and context-specific relationships between health worker and family member are key to understand and account for so that appropriate sensitization and implementation methods can be used. Ensuring adequate health worker education and knowledge of KMC is important in the West African context so as to support the female relatives' buy-in and acceptance.

Our findings support those from other African studies that carrying a newborn in front is viewed as representative of Western customs is contrary to traditional African newborn practices and is a potential barrier to KMC practice (Chan et al., 2016; Smith et al., 2017). Those aspects of KMC which are incongruous with local practice, such as carrying the newborn on the front, should be sensitive to their potential cultural implications and efforts should be made to include the biomedical explanations and benefits in community and hospital-based KMC sensitization activities.

Our findings around the need to protect newborns from the bad air or evil spirits reflect a common traditional belief in The Gambia and elsewhere that "foul wind" may be harmful to newborns and it is necessary to cover and protect the baby from *Jinne* or illness (Baum et al., 2012; O'Neill et al., 2017). Protecting small newborns by securing the baby in KMC position with a wrapper is consistent with these traditional beliefs and is a potential enabler to promote KMC practice. Kumar and colleagues (2008) used a similar technique in India for the improvement of newborn survival by merging key messages with existing beliefs and practices to facilitate behavior change.

Women undertaking caring responsibilities for family members have previously been described as "women in the middle of competing role demands, competing generations, and competing emotions" (Roe et al., 1994). This is reflected in our observation that women's postnatal responsibilities are centered on the care and support of the newborn and mother, but also encompass domestic and agricultural obligations within the intergenerational household sphere. Navigating these competing roles and understanding how KMC practice impacts women's postnatal responsibilities is essential for KMC programs and to promote continuation of KMC after hospital discharge. We identified that KMC is consistent with women's expected responsibilities but the impact for those with agricultural livelihoods should be considered further and opportunities for encouraging task-shifting within the family or household explored. Although impact on domestic chores is a well described barrier to KMC (Seidman et al., 2015; Smith et al., 2017), the negative effects on KMC practice have not been established in previous research (Nguah et al., 2011) and support from female relatives is an important mitigating factor.

The study has several strengths. It provides a detailed insight into perceptions of a previously underrepresented population around important newborn care practices. Despite the small sample size, thematic saturation was reached, and the findings provide a rich and detailed understanding of women's perceptions of newborn care in contemporary West Africa. The findings are transferable to other contexts with similar polygamous, patrilineal, and multigenerational household structures and gendered societal expectations. The data are dependable due to research and operational techniques and adheres to established trustworthiness criteria (Tuckett, 2005).

However, because KMC was not routinely practiced at time of the study, the findings reflect female relative's perceptions rather than their direct experience or behaviors. Thus, it provides insight for a setting which is KMC-naïve. Given the small sample size, these participants represent only a subsection of relatives who were willing to participate, and hence generalizability may be limited to female relatives already engaged with the hospital and invested in the care of their relative's newborn. Thus, the findings may not be representative of other female relatives in the community or those who choose not to accompany their relatives to hospital. Social desirability bias is also a risk due to the association of the interviewers with a locally well-regarded research institution (Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine [MRCG]) and with the hospital. The interviews were coded by a single researcher which may have led to the analysis being shaped by her own perspectives and understanding.

Maternal perceptions of newborn care and KMC are well-documented, but further research is required to understand fathers' perceptions, as their influence and support for mothers and female relatives is also key to the success of antenatal and postnatal health programs (Audet et al., 2016). For a holistic understanding of barriers and enablers to KMC in West Africa, the voices of other key stakeholders such as health workers, policy makers, community and religious leaders are also needed to encourage participation and buy-in with the aim of supporting further KMC roll-out. Further understanding

of the interpersonal and power dynamics between health workers and families would provide valuable insights for behavioral sciences and implementation science approaches to promoting KMC uptake.

Conclusion

We identified that in the Gambian context, female relatives of hospitalized small newborns accept KMC and are willing to both provide KMC themselves and support the mother with her postnatal responsibilities. Our findings add to the evidence that mothers in Africa are not autonomous decision makers, and female relatives are important stakeholders in newborn care decision-making and practices. Recognition of the importance of female relatives may create more holistic, family-centered approaches to implementation of newborn public health interventions. These women's voices have the power to identify and address barriers and enablers for more widespread adoption of KMC as a life-saving intervention for small, vulnerable newborns.

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Author Contributions

H.B. and M.D. conceived of and designed the study and interview questionnaire. M.D. and B.J. collected the data. M.D. conducted the analysis and wrote the first draft of the manuscript. H.B. gave substantial input to the manuscript, and all authors reviewed and gave inputs to the final manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval and Consent to Participate

Ethical approval was obtained from the ethics committees at London School of Hygiene & Tropical Medicine (LSHTM; Ref. 12398) and The Gambia Government/Medical Research Council Joint Ethics Committee (Ref. 1535). Written informed consent was obtained prior to participation, including consent for audio-recording.

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Availability of Data and Materials

Selected quotes and data generated during this study are included in this article.

Supplemental Material

Supplemental Material for this article is available online at journals.sagepub.com/home/qhr/10.1177/1049732320976365

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Maura Daly is a Sexual and Reproductive Health Advisor with Médecins Sans Frontières. A midwife with 17 years' experience in various settings, she has a particular interest in maternal, reproductive and newborn health in humanitarian settings. She holds an MSc from London School of Hygiene & Tropical Medicine.

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Loveday Penn-Kekana is a medical anthropologist and assistant professor at the London School of Hygiene & Tropical Medicine (LSHTM) where she leads the Births Theme at the MARCH Centre (Maternal Adolescent Reproductive & Child Health) and works on maternal health and health systems evaluations. She previously worked for 10 years at the Centre for Health Policy at the University of the Witwatersrand, South Africa, leading a number of projects focusing on maternal health and health systems

Joy Elizabeth Lawn is an African-born, British-trained paediatrician and perinatal epidemiologist with 30 years' experience including: clinical newborn care, epidemiological burden estimates, design and evaluation of maternal, newborn and child care services at scale, especially in sub-Saharan Africa. She is currently Director of the MARCH Centre (Maternal Adolescent Reproductive & Child Health) at London School of Hygiene & Tropical Medicine. She has published >280 peer-reviewed papers including leading several influential Lancet series, with wide media and policy uptake.

PHD OBJECTIVE 2

To investigate the effect of early KMC on survival and other clinically important outcomes, including safety, for unstable neonates <2000g

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Chapter 5 - Methods for a randomised controlled trial of early kangaroo mother care for unstable neonates (Article 2)

5.1. Scope of the chapter

This chapter provides detailed information on the methods of the eKMC randomised controlled trial to investigate survival and clinical effects of early KMC in mild-moderately unstable neonates <2000g.

5.2. List of figures

5.3. Supplementary material

The supplementary material detailed in the published article includes the adapted Stability of Cardio-Respiratory in Prematurity Score (SCRIP) definition (Annex A-5-1) and the SPIRIT checklist (Annex A-5-2).

5.4. Citation

Brotherton H, Gai A, Tann CJ, Samateh AL, Seale AC, Zaman SMA, Cousens S, Roca A, Lawn JE. **Protocol for a randomised trial of early kangaroo mother care compared to standard care on survival of pre-stabilised preterm neonates in The Gambia (eKMC).** Trials, 2020. 21(1): 247. doi: 10.1186/s13063-020-4149-y

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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	1601409	**Title**	Dr
First Name(s)	Helen		
Surname/Family Name	Brotherton		
Thesis Title	Early Kangaroo Mother Care for mild-moderately unstable neonates <2000g in The Gambia		
Primary Supervisor	Joy Lawn		

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: Brotherton H, Gai A, Tann CJ, Samateh AL, Seale AC, Zaman SMA, Cousens S, Roca A, Lawn JE. Protocol for a randomised trial of early kangaroo mother care compared to standard care on survival of pre-stabilised preterm neonates in The Gambia (eKMC). Trials, 2020. 21(1): 247. doi: 10.1186/s13063-020-4149-y		
When was the work published?	6 March 2020		
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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 conceived of the research idea in collaboration with my lead supervisor (Joy Lawn) and obtained funding for the trial through successfully obtaining a Wellcome Trust Research Training Fellowship. I led the development and design of the trial protocol with input from Joy Lawn, Syed Zaman, Simon Cousens, Anna Seale, Anna Roca and Cally Tann. I led the research team in trial preparation and implementation with assistance from Abdou Gai, Bunja Kebbeh, Georgia Walker and Ahmadou Lamin Samateh. I led the drafting of the manuscript, incorporated feedback from co-authors and co-ordinated submission and response to peer-reviewers comments.

SECTION E

Student Signature	Helen Brotherton
Date	30th June 2021

Supervisor Signature	Joy Lawn
Date	6th July 2021

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Trials

STUDY PROTOCOL Open Access

Protocol for a randomised trial of early kangaroo mother care compared to standard care on survival of pre-stabilised preterm neonates in The Gambia (eKMC)

Helen Brotherton[1,2,3*], Abdou Gai[2], Cally J. Tann[1,4,5], Ahmadou Lamin Samateh[6], Anna C. Seale[1], Syed M. A. Zaman[7], Simon Cousens[1], Anna Roca[2] and Joy E. Lawn[1]

Abstract

Background: Complications of preterm birth cause more than 1 million deaths each year, mostly within the first day after birth (47%) and before full post-natal stabilisation. Kangaroo mother care (KMC), provided as continuous skin-to-skin contact for 18 h per day to fully stabilised neonates ≤ 2000 g, reduces mortality by 36–51% at discharge or term-corrected age compared with incubator care. The mortality effect of starting continuous KMC before stabilisation is a priority evidence gap, which we aim to investigate in the eKMC trial, with a secondary aim of understanding mechanisms, particularly for infection prevention.

Methods: We will conduct a single-site, non-blinded, individually randomised, controlled trial comparing two parallel groups to either early (within 24 h of admission) continuous KMC or standard care on incubator or radiant heater with KMC when clinically stable at > 24 h of admission. Eligible neonates (n = 392) are hospitalised singletons or twins < 2000 g and 1–24 h old at screening who are mild to moderately unstable as per a trial definition using cardio-respiratory parameters. Randomisation is stratified by weight category (< 1200 g; ≥ 1200 g) and in random permuted blocks of varying sizes with allocation of twins to the same arm. Participants are followed up to 28 ± 5 days of age with regular inpatient assessments plus criteria-led review in the event of clinical deterioration. The primary outcome is all-cause neonatal mortality by age 28 days. Secondary outcomes include the time to death, cardio-respiratory stability, hypothermia, exclusive breastfeeding at discharge, weight gain at age 28 days, clinically suspected infection (age 3 to 28 days), intestinal carriage of extended-spectrum beta-lactamase producing (ESBL) *Klebsiella pneumoniae* (age 28 days), and duration of the hospital stay. Intention-to-treat analysis will be applied for all outcomes, adjusting for twin gestation.

Discussion: This is one of the first clinical trials to examine the KMC mortality effect in a pre-stabilised preterm population. Our findings will contribute to the global evidence base in addition to providing insights into the infection prevention mechanisms and safety of using this established intervention for the most vulnerable neonatal population.

Trial registration: ClinicalTrials.gov NCT03555981. Submitted 8 May 2018 and registered 14 June 2018. Prospectively registered.

Keywords: Preterm, Neonate, Kangaroo care, Kangaroo mother care, Skin-to-skin contact, Survival, Infection, Randomised controlled trial, Pragmatic

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Background

Every year an estimated 14.8 million neonates are born preterm (< 37 completed weeks of gestation), of which > 80% are in Asia or Sub-Saharan Africa [1], and more than 1 million die due to complications of prematurity [2]. An estimated 47% of all prematurity-related deaths in resource-limited settings occur within the first day after birth [3] before post-natal stabilisation is complete. This is the critical period in which to target interventions to improve preterm survival and accelerate progress toward the Sustainable Development Goal (SDG) target 3.2 for neonatal mortality reduction. More than 40 countries, many in sub-Saharan Africa, need to more than double their current progress to meet the target by 2030 [4].

Kangaroo mother care (KMC) is an evidence-based package recommended as standard care for all clinically *stable* (pre-stabilised) neonates < 2000 g [5], which is the proxy weight used in previous KMC trials as an indicator for preterm birth [6]. Described in Colombia four decades ago, KMC has since been widely adopted as a cornerstone of neonatal care. The key component is prolonged, skin-to-skin contact between neonate and caregiver, facilitating exclusive breastmilk feeding and shorter hospital stay [7].

Clinical stability is variably defined in previous KMC trials with no standardised WHO definition or validated clinical model for resource-limited settings. In neonates < 2000 g who have completed stabilisation or post-natal transition, continuous KMC (aiming for > 18 h/day) reduces mortality at discharge or 40 weeks post-menstrual age by 36–51% [6, 8, 9] compared to incubator care, with the mortality effect observed only in resource-limited settings [6]. However, an evidence gap exists for neonates yet to complete stabilisation, who have greatest risk of death or adverse outcome [6]. In 20 trials that assessed mortality at latest follow-up and were included in three systematic reviews [6, 8, 9], KMC was initiated at an average age ≤ 4 days in seven trials, with only one RCT starting continuous KMC in pre-stabilised neonates within 24 h after birth [10]. This Ethiopian trial reported a 40% reduction in mortality (RR = 0.57, 95% CI 0.33–1.00, $p < 0.05$) but more than half of the unstable neonates were excluded, and the eligibility criteria were unclear, leading to high risk of bias [6, 10].

KMC is a safe intervention for unstable neonates in resource-rich settings with intensive monitoring [11], but the safety profile in a context of less close clinical monitoring is not established [6] and warrants further scrutiny.

KMC works through multiple pathways, many mediated by skin-to-skin contact [12], including thermal control [6], neuro-endocrine mechanisms involving oxytocin release in both mother and neonate [12], reduced cortisol and stress response [13], cardio-respiratory stabilisation [14], enhanced breast milk production [6] and empowerment of the KMC provider in caring for their baby. Alterations in the neonatal microbiome with intermittent KMC have also been reported [15] and warrant further exploration to understand the infection prevention effects of KMC. The relevance and relative contribution of these mechanisms for KMC in pre-stabilised neonates are unknown, particularly for infection prevention outcomes, which is an evidence gap for all preterm neonates.

The eKMC trial aims to investigate continuous KMC in pre-stabilised neonates < 2000 g in a Gambian health facility setting. A secondary aim is to explore potential underlying mechanisms of KMC in this high-risk population.

Objectives

The primary objective of the eKMC trial is to assess the effect of early continuous KMC on the survival of pre-stabilised preterm neonates.

Secondary objectives

Secondary objectives include the following:

1. Assess the effect of early continuous KMC on other important clinical outcomes (growth, late-onset infections and duration of hospital stay)
2. Evaluate the safety of providing early continuous KMC to pre-stabilised preterm neonates in a resource limited facility setting
3. Explore possible mechanisms for hypothesised beneficial effects of early continuous KMC in pre-stabilised preterm neonates, focusing on infection prevention

Methods/design

This article has been prepared according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Additional file 1) [16].

Study design

This single-site, pragmatic, non-blinded, individually randomised superiority trial compares two parallel groups managed with either continuous KMC started within 24 h of hospital admission or standard care with intermittent or continuous KMC when clinically stable > 24 h after admission. The unit of randomisation is the mother in a 1:1 ratio with twin participants randomised to the same arm.

Study setting and context

Recruitment began on 23 May 2018 and is ongoing at the neonatal unit of Edward Francis Small Teaching Hospital (EFSTH), the main neonatal referral unit in The Gambia, with research support from the MRC Unit

of Gambia at London School of Hygiene & Tropical Medicine (MRCG at LSHTM).

The Gambia is the smallest country in mainland Africa, with a population of 2.1 million, and it is ranked 174/189 on the Human Development Index (2017) [17]. Neonatal mortality declined from 49 to 26 per 1000 live births between 1990 and 2018, respectively [18], with 12–14% of Gambian neonates born preterm [1, 19] and 29% of neonatal deaths attributed to complications of prematurity [3].

A quarter (26%) of the 1400 annual neonatal admissions to EFSTH are due to prematurity [20], and the neonatal case fatality rate is 38%, with the highest rate (58%) occurring amongst neonates born < 1500 g [20]. Both in-born (born at the EFSTH maternity unit) and out-born (born at another health facility or home) neonates are admitted from a mixed rural/urban population.

Neonatal care is typical of secondary level "neonatal special care" [21] and includes management in incubators or under radiant heaters, respiratory support via oxygen concentrators or continuous positive airway pressure (bubble-CPAP), phototherapy, feeding support via gastric tubes and intravenous (IV) fluids, caffeine or aminophylline, phenobarbitone and broad-spectrum antibiotics. Invasive ventilation, surfactant, IV fluid pumps and continuous cardio-respiratory monitoring are unavailable. Continuous KMC was implemented as standard care during the formative trial phase in September 2017. Intermittent KMC is provided for a minimum of 60 min at periodic intervals on the neonatal unit once the neonate is off respiratory support and establishing enteral feeds. Neonates < 2000 g receive continuous KMC on an adjacent eight-bed KMC unit once they are stable in room air, are tolerating full enteral feeds and have a willing caregiver available. Neonates are transferred to the KMC unit at average 10 days of age (n = 148, SD 7.8) with the average KMC unit admission lasting for 6.9 days (n = 108, SD 4.0) and 92% (141/151) of discharged neonates attend hospital follow-up at least once, on average 7.5 days after discharge (n = 141, range 2–23 days) (unpublished audit data, Sept. 2017 to May 2018, H. Brotherton).

Study population and procedures

Enrolment, interventions and assessments are outlined in Fig. 1.

The study population is hospitalised neonates < 2000 g and age 1–24 h old at the start of the screening who meet the trial definition of mild-moderate instability based on cardio-respiratory parameters and respiratory support provision (Fig. 2).

Inclusion criteria are as follows:

- New admission of singleton or twin (inborn or outborn)
- Weight < 2000 g as per study scale
- Age 1–24 h old when screening begins
- Mother or other caregiver available and willing to provide intervention

Exclusion criteria are as follows:

- Triplets who are all admitted to the study site
- Congenital malformation not compatible with life or needing immediate surgical intervention
- Severe jaundice
- Seizures
- Stable as assessed during cardio-respiratory screening
- Severely unstable as assessed during cardio-respiratory screening or died during screening
- No study bed available
- Neonates/mothers enrolled in another research study
- No written informed consent from parent or caregiver within 24 h of admission.

Screening for eligibility

Eligibility is assessed in all admitted neonates with referral weight ≤ 2000 g as soon as possible and once > 1 h old. Weight is confirmed using a calibrated SECA™ 757 digital weighing scale, and source documents are checked for age and other study involvement. All potentially eligible neonates aged < 24 h undergo an examination with cardio-respiratory stability assessed over 10 min using Nonin™ 2500A pulse oximeter.

Stable neonates are excluded as it is considered unethical to randomise them to a proven intervention. Mildly unstable neonates are immediately eligible for recruitment. Moderately or severely unstable neonates undergo continuous pulse oximetry with a repeat stability assessment 3 h later. Severely unstable neonates are excluded at the repeat 3 h screening, as it is not possible to provide KMC alongside resuscitation or CPAP at the study site (Fig. 2). Clinically eligible neonates are recruited if a study bed is available and a caregiver is willing to both provide the intervention (if applicable) and give written consent within 24 h of hospital admission. If eligibility criteria are met but the caregiver is only available > 3 h after the end of cardio-respiratory screening, stability is re-checked prior to consenting to avoid inadvertent recruitment of stable or severely unstable patients. Standard care under radiant heater or incubator is provided to all neonates during the screening period.

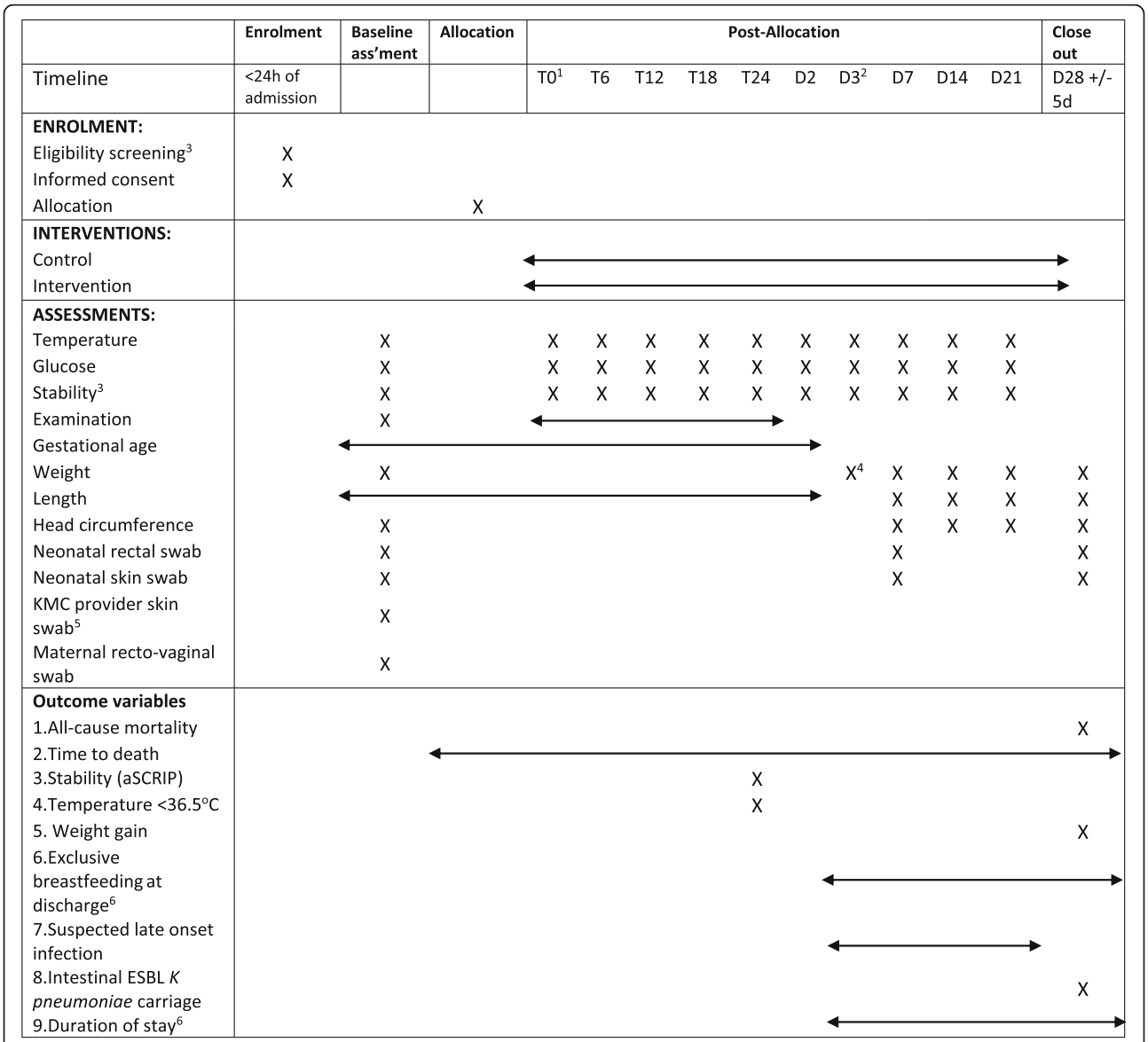
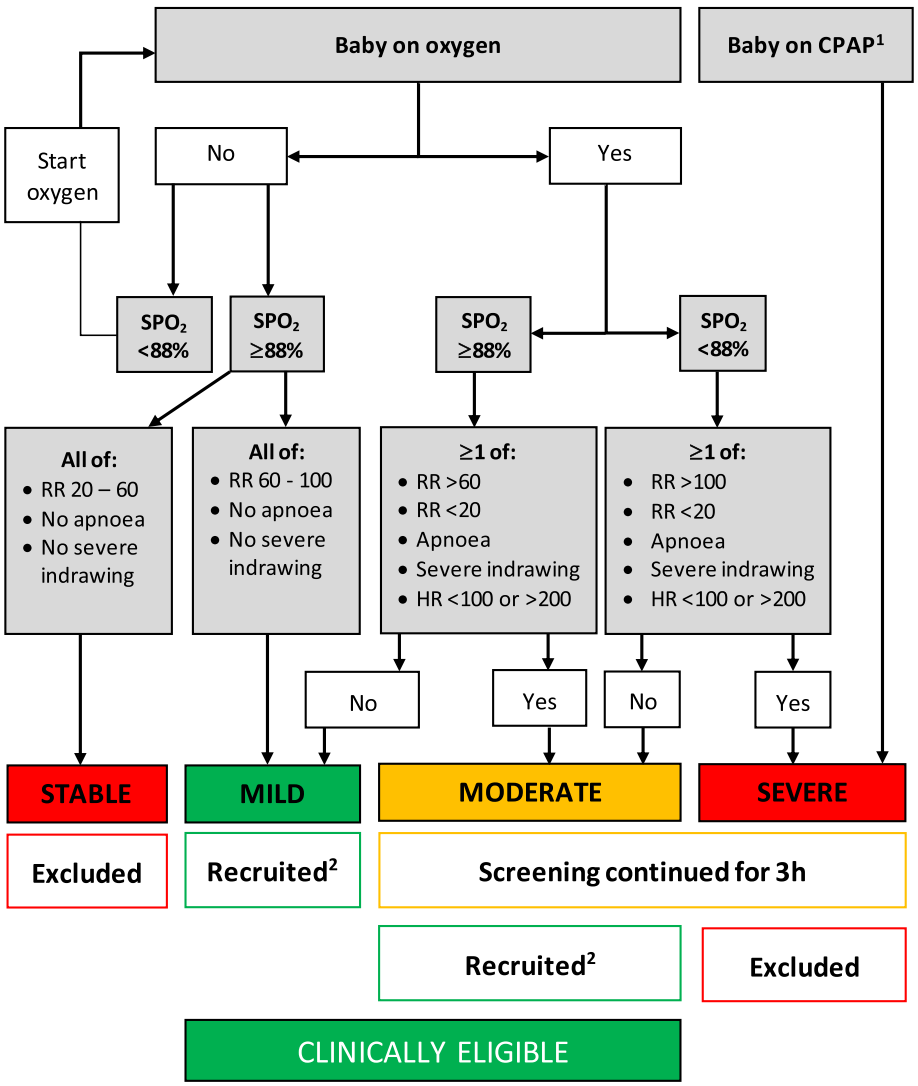


Fig. 1 eKMC trial schedule of enrolment, interventions and assessments [16] 1. The start of study procedures (Time 0) is defined as when the pulse oximeter is attached for baseline continuous cardio-respiratory assessment, immediately prior to the intervention/control procedures commencing. 2. Participants are reviewed daily until KMC unit admission, after which they are reviewed on days 7, 14, 21, and 28 of age whilst inpatients and on day 28 as outpatients. Daily reviews are re-started if the baby is transferred back to the neonatal unit. 3. Stability definitions used during eligibility screening and routine assessments are detailed in Fig. 2. 4. Weight at 5 days of age is taken on calibrated digital scales and then is taken daily until either discharge or KMC unit admission, after which it is obtained on days 7, 14, 21, and 28 whilst an in-patient and at the day 28 follow-up if discharged. 5. Skin swab samples are taken from the first person to provide skin-to-skin contact and the mother (if different) as soon as possible and prior to any skin-to-skin contact. The relationship of the KMC provider to the participant is documented and correlated with swabs using unique, anonymised identification codes. 6. Outcomes such as feeding method and duration of stay are recorded at the time of discharge, including for participants hospitalised for > 28 days

Consent

Sensitisation activities with health workers, pregnant women and families are conducted at referral health facilities to support recruitment. Written, informed consent for participation and provision of continuous KMC (in event of randomisation to intervention arm) is sought from the first available caregiver at the study site within 24 h of admission by trained study personnel. The parent is the preferred person to provide informed consent, but other relatives may provide consent with parental informed consent being sought as soon as possible. Consent is requested in English with verbal translation into local languages using a pre-designated dictionary of definitions. Impartial witnesses are used to support the consenting



CPAP=Continuous positive airway pressure, provided as bubble CPAP; RR=Respiratory rate; h=hours; HR=Heart rate; SPO_2=oxygen saturation

Fig. 2 eKMC trial definitions of cardio-respiratory instability and eligibility status. 1. Criteria for starting CPAP is a Silverman-Anderson score ≥ 4 that does not improve with oxygen therapy and the absence of the following: heart rate < 100 bpm, floppy tone and seizures. 2. The neonate is recruited if a study bed is available and consent is provided by a willing caregiver

process with caregivers who are unable to read or write English. Consent for obtaining and future use of paired maternal recto-vaginal and skin swab samples from the first KMC provider and mother (if different) is sought before any skin-to-skin contact occurs.

Randomisation, allocation and blinding

An independent statistician generated a randomisation sequence using VBA (Visual Basic Application) within an Access database to produce two random number tables with stratification by admission weight categories (< 1200 g or ≥ 1200 g). Random permuted blocks of varying block sizes were used in a 1:1 allocation. The allocation sequence is concealed with sequentially numbered, opaque, sealed envelopes prepared by an independent researcher and accessible to study team only. Following the collection of baseline data, the study nurse opens the next numbered envelope for the correct weight category. The participant identifier, date and time are recorded on the outside of the envelope prior to opening, to identify any subversion of allocation sequence. Twins are allocated to the same arm, according to the first eligible twins' weight.

Given the nature of KMC, blinding parents/caregivers and study personnel to the allocation arm and the

primary outcome is not possible. Process and secondary outcome data will be anonymised, and all analyses will be blinded.

Intervention

The terms KMC and skin-to-skin contact are used as synonyms in the literature, but the intervention under study is continuous skin-to-skin contact between neonate and caregiver started within 24 h of admission. The neonate is naked except for nappy and woollen hat and is secured with a Thari wrapper (customised KMC wrapper developed in South Africa) in a prone, frog-leg position on caregivers' naked chest with head turned sideways (Fig. 3).

The caregiver sits or lies down whilst the neonate receives all other treatments (oxygen via nasal prongs, intravenous (IV) fluids via peripheral venous cannula, gastric tube feeds and IV medications). If the mother is unavailable, other relatives (e.g., fathers or grandmothers) provide the intervention. KMC is advised for as long as possible, aiming for ≥ 18 h/day. When not receiving KMC, the baby remains in an incubator or under a radiant heater in the same room, with co-habitation of the radiant heater. If participants meet clinical "stopping criteria" (Fig. 4c), participants are temporarily withdrawn from the intervention arm, receive standard incubator or radiant heater care and re-start KMC once the stability criteria are met (Fig. 4d)

Fig. 3 An eKMC participant receiving the intervention of ocntinuous skin-to-skin contact at the same time as other standard care treatments (H.Brotherton with caregiver consent for publication)

Control

The neonate is managed in an incubator or under a radiant heater, naked except for a woollen hat and nappy or wrapped in a cloth. The parent/caregiver can touch, hold and feed the neonate as per standard practice but skin-to-skin contact is not provided until stability criteria are met (Fig. 4d) and after > 24 h since hospital admission. Participants then receive intermittent KMC on the neonatal unit and continuous KMC on the adjacent KMC unit (Fig. 4d).

Flow around study site for both arms

After their baseline stability data have been collected, all participants are transferred to a "trial area" within the neonatal unit containing four small beds, chairs, incubators, radiant heater and an oxygen concentrator. This area can accommodate 8–10 patients with twin participants sharing incubators. If a neonate subsequently becomes severely unstable (Fig. 2), the affected participants are transferred to the high dependency area and then follow the standard flow around the neonatal unit. Neonates are moved from "trial area" to the KMC unit once stability criteria are met (Fig. 2), full enteral feeds have been tolerated for the previous 12 h, no phototherapy is required and both a willing caregiver and KMC unit bed are available. If participants become unwell whilst on the KMC unit, they are re-admitted to the neonatal unit and follow the standard patient flow.

Clinical management and study procedures for neonates in both arms

Baseline anthropometric and clinical data are collected prior to randomisation with the exception of gestational age and length (within 48 h of recruitment) and socio-demographic data (within 28 days). The first available caregiver is sensitised at baseline for infection control, provision of KMC, clinical danger signs and when to call for help. All other routine and emergency treatments, including discharge, are provided according to a standardised preterm management protocol, based on pre-existing standard care at the study site and consistent with WHO guidelines. Compliance with the protocol is monitored prospectively by trial clinicians. Continuous monitoring of cardio-respiratory stability with a Nonin™ 2500A pulse oximeter occurs for a minimum 24 h of study participation, until stability is reached (Fig. 2). Direct nursing observation documents all details of the KMC provided, including the date and time of first KMC contact, relationship with the person providing KMC, KMC session frequency and duration, number of

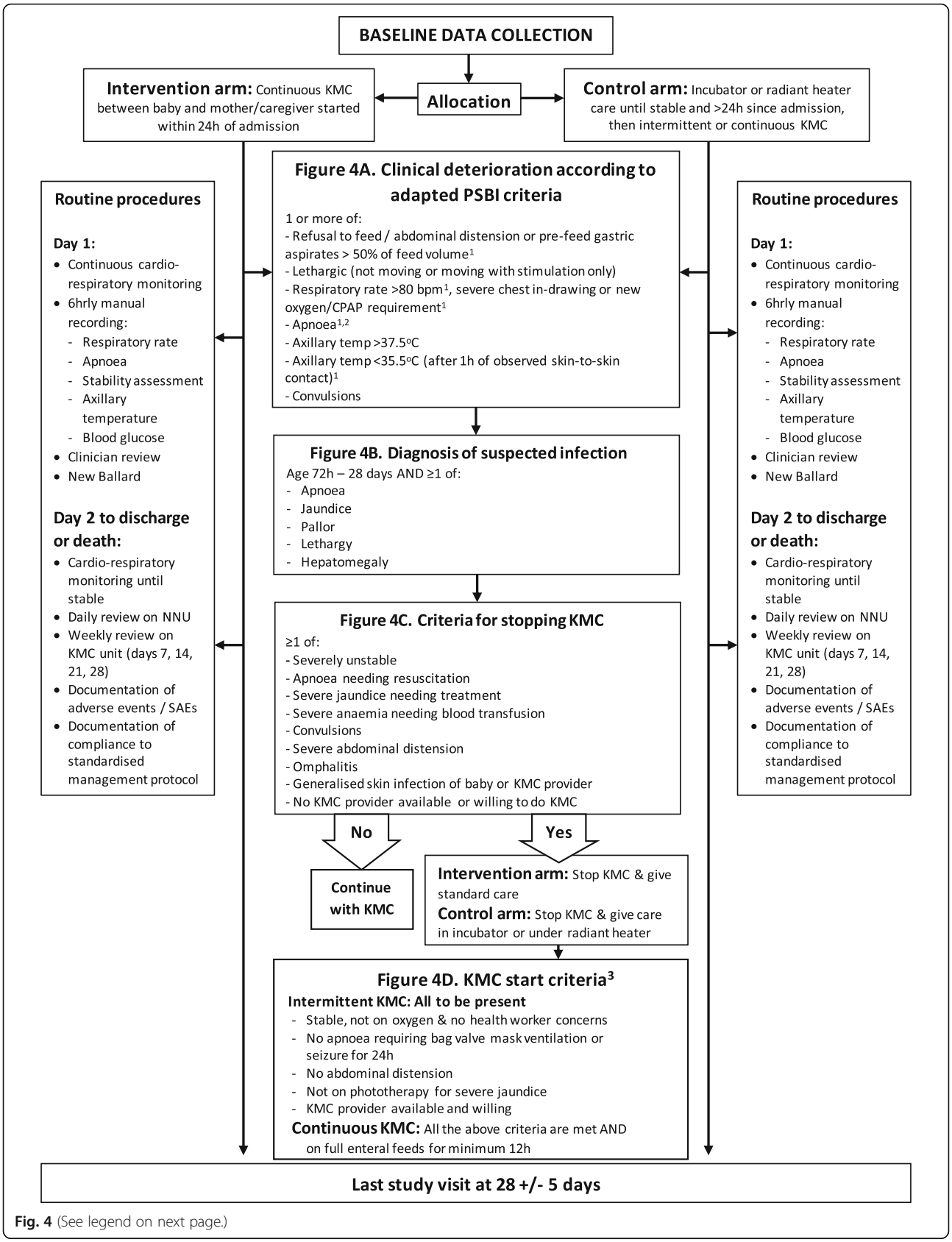


Fig. 4 (See legend on next page.)

(See figure on previous page.)
Fig. 4 Overview of eKMC routine procedures and assessment of clinical deterioration including key trial criteria. 1. New or changed PSBI definitions to increase relevance for hospitalised preterm neonates. 2. Spontaneous apnoea with no identifiable reason, e.g., not associated with milk aspiration or end-stage respiratory failure. 3. Re-start criteria also apply to neonates in control arm at the initiation of KMC

neonates receiving KMC from the same provider and the reason for not providing KMC.

Structured study reviews occur with decreasing intensity as stability improves, with reviews every 6 h for the first 24 h, daily reviews whilst on the neonatal unit and weekly reviews during the KMC unit admission (Fig. 4). The final study review at 28 ± 5 days of age occurs at EFSTH, with home visits for non-attenders. Caregivers may withdraw from the study at any time. Data collected up to the point of the most recent follow-up within 28 ± 5 days of age will be included in the analyses.

Outcome measures

Primary outcome

The primary outcome is all-cause mortality at age 28 days.

Secondary outcomes

Secondary outcomes include the following:

1. **Time from start of study procedures to death**
   The date and time of death is recorded as soon as possible using the death certificate as a source document for in-hospital deaths and according to the caregiver verbal report for out-of-hospital deaths.
2. **Cardio-respiratory stability at 24 h of study participation (aSCRIP score)**
   The Stability of Cardio-Respiratory in Preterm Infants (SCRIP) score is an objective measure of stability used in previous KMC trials [14, 22]. The score was modified for relevance to a pre-stabilised preterm population receiving oxygen (Additional file 2).
3. **Prevalence of hypothermia (axillary temperature < 36.5 °C) at 24 h of study participation**
   Axillary temperature is measured with an electronic thermometer as the average of three consecutive values.
4. **Proportion of neonates exclusively breastfeeding at the time of discharge**
   Exclusive breast-feeding and use of formula milk are recorded prospectively by direct observation and questioning of caregiver at time of discharge.
5. **Mean daily weight gain at age 28 ± 5 days (g/day)**
   This gain is the difference in weight between baseline and day 28 ± 5 days, as measured on a calibrated study scale.
6. **Incidence of clinically suspected infection from 3 to 28 days of age or latest follow-up**
   In the absence of a standardised clinical definition for infection in preterm neonates, a two-step process is used to identify clinically suspected infection (Fig. 4a & b). The WHO's Possible Serious Bacterial Infection (PSBI) criteria [23] were adapted to increase the relevance to a hospitalised preterm population receiving KMC (Fig. 4a). If any aPSBI criteria are present, a clinician examines the baby for features of suspected infection [24] (Fig. 4b), and blood ± cerebro-spinal fluid (CSF) cultures are obtained if these criteria are met. *BACTEC Peds* Plus™/F vials are inoculated with minimum 1 ml venous blood by study clinicians and processed as soon as possible within 24 h in an automated Bactec® 9050 BD machine at MRCG at LSHTM. Samples with positive signal undergo sub-culture as per standard culture methods, species identification by API 80 system and antibiotic susceptibility testing by disc diffusion according to CLSI 2017 guidelines. CSF samples are collected by study clinicians as soon as possible and in the absence of contra-indications. CSF is transported to MRCG laboratories at room temperature within 1 h of collection for routine microbiological and biochemical analysis. Isolation of clinically significant bacteria are recorded, with coagulase negative staph (CONS) and bacillus species predefined as non-pathogenic. A secondary analysis of the effect of KMC on confirmed (culture positive) infection is planned.
7. **Prevalence of neonatal intestinal carriage of extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* at age 28 ± 5 days**
   Rectal swabs are taken with size appropriate FLOQ™ swabs and stored for batch microbiological processing. Additional paired maternal and/or caregiver-neonatal carriage flocked swab samples obtained at baseline, 7 days (neonatal) and 28 ± 5 days (neonatal) (Fig. 1) are stored for future microbiological and molecular processing.
8. **Mean duration of stay (hours)**
   Time from study site admission to discharge is documented prospectively according to source documents for the first admission episode. This information indicates if a participant is discharged after 28 days of age.

Other variables of interest

Adverse events (e.g., abnormal blood glucose, jaundice, apnoea) are observed in both arms as safety parameters.

The number, proportion and reason for temporary withdrawal from the intervention arm is recorded. Weekly anthropometry (weight, length and head circumference) provides additional indicators of growth. Continuous heart rate and oxygen saturation measurements alongside 6-hourly aSCRIP scores (Additional file 2) are recorded for the first 24 h of study participation for a planned secondary analysis of cardio-respiratory stability.

Data collection, management and security

All study personnel are trained in ICH-GCP, study objectives and study-specific procedures, in addition to being trained in clinical newborn care and KMC. Sociodemographic, clinical and summary laboratory data are collected using the REDCap™ data entry system with built-in range and consistency checks. Length is obtained with a Seca210 measuring mat and head circumference with non-stretchable tape measures using triplicate measures and regular inter- and intra-observer standardisation checks with double-blind assessments against clinician assessment. Vital signs are measured over 10-min periods to generate mean values, using calibrated Nonin™ 2500A pulse oximeters for heart rate and oxygen saturation with manual recording of respiratory rate. Gestational age assessment is done by trained clinicians using the New Ballard [25] score with regular inter-observer variability monitoring. All biological samples are processed or stored (maximum -70 °C) at MRCG at LSHTM laboratories and biobank (ISO 15189 Accredited), including paired neonatal-caregiver carriage swab samples and invasive isolates intended for future exploration of infection mechanisms. Cardio-respiratory stability data from Nonin™ 2500A pulse oximeters is downloaded, analysed with NVision™ software and reconciled with the study database. The daily dose of KMC is automatically calculated before reconciliation with the study database. All data are securely stored on a MRCG central server or at the study site with restricted access. A non-identifiable unique study number for neonate and caregiver is used to maintain confidentiality for all data, including stored samples, with linkage of neonatal and caregiver identifications.

Sample size

A total of 392 subjects (1:1 ratio) is required to detect a 30% relative reduction in the primary outcome (power 80%, alpha = 0.05) with recruitment planned for 2 years. This number is based on an expected mortality rate of 48% [20], with adjustment for an estimated 15% reduction in mortality due to trial implementation. Loss to follow-up rates are expected to be low (< 3%) due to the restricted geographical area, co-ordination of follow-up with routine appointments and re-imbursement of travel expenses.

Statistical analyses

A detailed statistical analysis plan will be made available at the trial registry before analysis commences. Analysis of all outcomes will be on an intention-to-treat basis. Since complete twin allocations account for an estimated 20% of the study population and are independent risk factors for mortality [26], adjustment for twin correlation will be undertaken using linear mixed effects models for continuous data and generalised estimating equations for binary data.

Comparability of participants in two arms

Baseline characteristics will be presented by the allocation arm using descriptive statistics. Key indicators of standard hospital care received will be compared for both arms at baseline and during admission.

Flow of participants

The number and flow of subjects through screening, randomisation, allocation, follow-up and analysis will be documented, as per CONSORT 2010 guidelines [27], with reasons for exclusion, withdrawal and non-analysis being described (Fig. 5). Participants will be excluded from the final analysis if they have been permanently withdrawn.

Primary and secondary outcome analysis

The number of subjects with the primary outcome will be calculated for each arm and generalised estimating equations used to calculate risk ratios and the number needed to treat with confidence intervals. Analysis of secondary outcomes will be performed according to the type of data and using either number of subjects or person time as the denominator. Continuous variables will be compared between arms using random effects models, and categorical data with generalised estimating equations. Survival analysis of the time to death within first 28 days after birth will be performed using cox regression with frailty. In the event of multiple events for the same participant (e.g., infection), each episode will be considered an isolated event.

Missing data are expected to be few and will be addressed with a complete case analysis. Sub-group analyses for all outcomes will be performed according to birth weight categories (< 1200 g; ≥ 1200 g) and multiple birth. Tests for effect modification by weight and multiple birth will be performed. The following will be calculated for both arms as indicators of adherence: mean chronological age at first KMC contact, mean time since admission at first KMC contact, daily dose of KMC (hours per study day) and average daily dose of in-

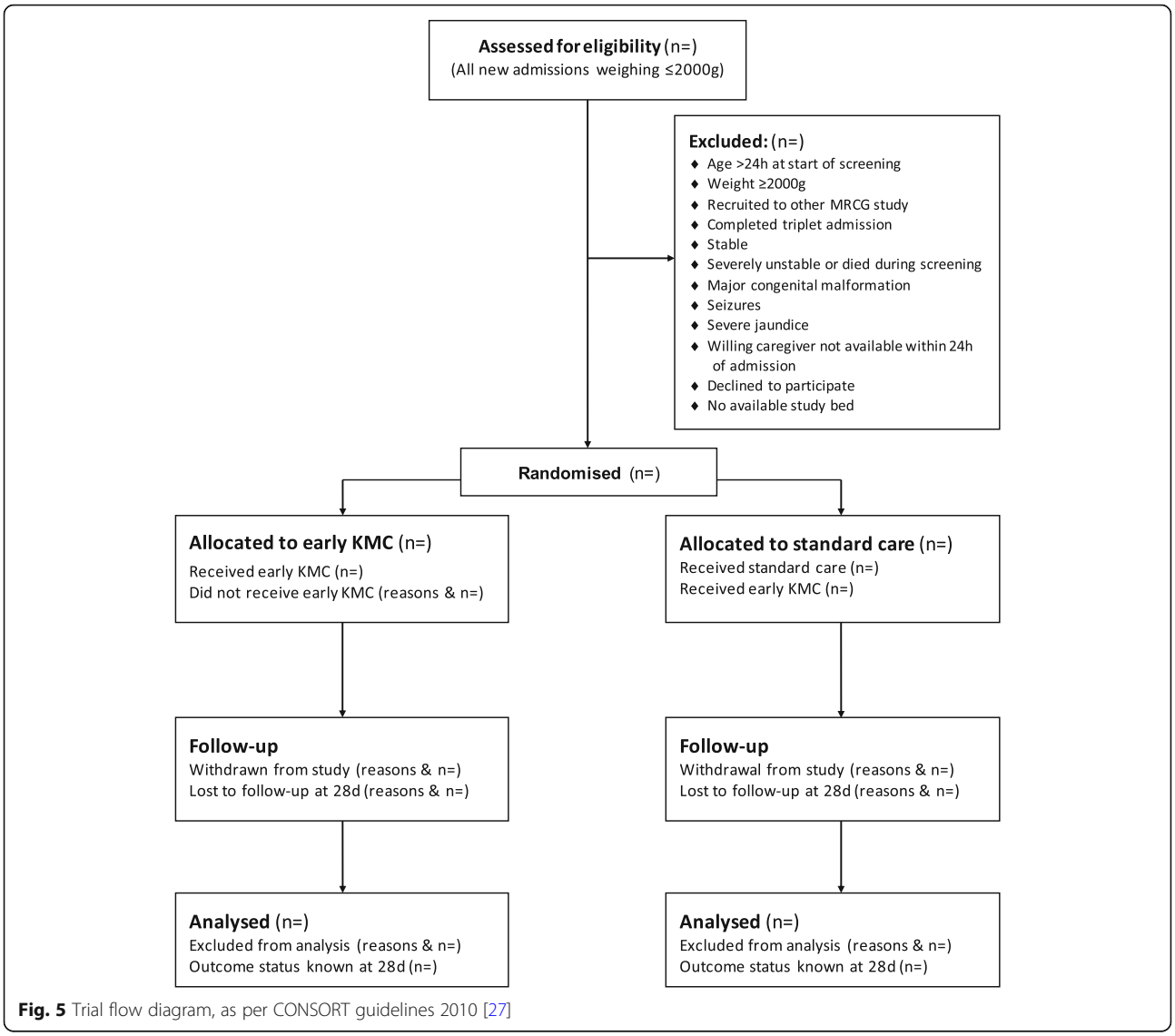


Fig. 5 Trial flow diagram, as per CONSORT guidelines 2010 [27]

patient KMC (per number of days admitted from enrolment). A sensitivity analysis of all outcomes will be performed according to average in-patient daily dose of KMC.

Safety reporting and study monitoring against ICH-GCP standards

Adverse events are any clinical event resulting in a change in management of the participant after enrolment and until age 28 days. Serious adverse events (SAE) are defined as death, life-threatening events (e.g., apnoea requiring bag-valve-mask ventilation, or severe instability), events carrying a risk of permanent or temporary disability (e.g., suspected meningitis), re-hospitalisation within 28 days of age and prolonged hospitalisation for ≥ 28 days.

A local safety monitor, the sponsor and the trial monitors are informed of all SAEs within 24 h of the study team being aware with a detailed report sent within 2 working days for fatal and 5 days for a non-fatal SAE. All fatal SAEs are reported to the ethics committees monthly and within 7 days if related to the intervention. Non-fatal SAE's are communicated to the ethics committees annually or within 14 days if related to the intervention. A Data Safety Monitoring Board (DSMB) receives a bi-monthly safety report with bi-annual meetings to monitor recruitment, progress and safety. DSMB members include the clinical trialist/statistician (chair), a neonatologist experienced in a similar setting, a West African clinical trialist and an independent statistician. An un-blinded interim analysis will be conducted after randomisation of 50% of target sample size with pre-specified stopping rules for efficacy, using the Haybittle-Peto rule [28, 29] and will inform recommendations to the Trial Steering Committee (TSC), who will make the

final decision on study continuation. Study procedures and documents are monitored for compliance to ICH-GCP standards by MRCG monitors every 3–6 months, with auditing determined by the sponsor.

Discussion

Evaluating the effect of continuous KMC before full stabilisation is a global research priority, stated by WHO [6] with the potential to contribute towards reducing the unacceptably high global neonatal mortality, enabling progress towards the neonatal mortality target SDG3.2 by 2030, as well as promoting a family-centred approach to newborn care. eKMC is one of the first trials to address this evidence gap and is expected to provide robust evidence in addition to novel mechanistic insights, particularly regarding infections, which are one of the major pathways to mortality for preterm neonates.

KMC reduces severe infections (6.6% vs 13.1%, RR = 0.5, 95% CI 0.36–0.69) and nosocomial infections (4% vs 11%, RR = 0.35, 95% CI 0.22–0.54) with intermittent or continuous KMC in stable neonates [6]. However, previous KMC trials have lacked clear case definitions for infection and a paucity of microbiologically confirmed data are available from resource-limited settings [6]. eKMC will contribute towards understanding the infection prevention effects of KMC by using a validated nosocomial risk score [24] microbiological testing and exploration of impact on carriage of antimicrobial resistant bacteria.

During eKMC trial piloting, we identified important challenges, which are outlined below with mitigating approaches:

Challenge 1 - Recruitment: The unavailability of caregivers willing to consent *and* provide the intervention within 24 h after birth is a major recruitment barrier due to high rates of maternal illness or post-caesarean section and absence of other family members at the hospital during the early admission period. Sensitisation activities with pregnant women and their families and health workers are undertaken at referral centres to encourage recruitment. A high proportion of either severe instability or death occurs before or during the screening process, reflecting the high proportion of out-born neonates and a vulnerable population. Access to sufficient study beds for the intervention was a limiting factor, and the number of study beds was increased from 2 to 4 during the piloting period to facilitate recruitment.

Challenge 2 - Non-blinded trial: KMC could not be blinded for the family or researchers. Selection and allocation bias are prevented through rigorous screening and randomisation procedures with objective stability markers, and transparent reporting of non-recruitment will be performed. Treatment bias is minimised via a protocolised approach to standard care with prospective monitoring of adherence, comparable clinical monitoring and caregiver education for both arms.

Challenge 3 - Twins: Like much of West Africa, the twin birth rate in The Gambia is high at 16.7/1000 live-births [30] with greater risk of premature delivery and neonatal death compared to singletons [26, 30]. Evaluation of the intervention in twins is essential for generalisability of results and to target the most vulnerable neonates. Investigators anticipate that 30% of participants will be twin gestation, with complete twin enrolment accounting for 20% of the study population. This may lead to differences in provision of the intervention in addition to independently impacting the trial outcomes. All efforts to adjust for multiple births will be made during analysis.

Challenge 4 – Improvements to standard care leading to potential dilution of the intervention effect and risk of inadequate power: Alongside externally driven improvements to newborn care at the study site, eKMC implementation has resulted in major improvements to standard care for both trial and non-trial neonates. In collaboration with the hospital, the Gambian Government Ministry of Health and Social Welfare and UNICEF The Gambia, an eight-bed KMC unit was established, and continuous KMC was embedded in standard care in 2017. A protocolised approach to standard care of preterm neonates was also introduced at the site to reduce the risk of treatment bias. Although highly beneficial from an individual patient perspective, these improvements in care are expected to reduce both the power of detecting a difference in the primary outcome and may reduce differences between allocation arms, diluting the intervention effect. These changes to standard care will be explored in a linked process evaluation, based on the MRC guidance for evaluation of complex interventions [31] and using data collected before and after trial implementation. Activities will include a survival analysis of neonatal case fatality rates using published data from the study site [20] and prospective data collection for all admissions over the trial period, tracking of the changes made to standard newborn care, and KMC implementation progress monitoring [32].

If early KMC for pre-stabilised neonates is shown to be beneficial, we need to understand how to implement in a real-world setting. eKMC-generated implementation and safety data will be valuable, particularly when combined with similar trials, such as the multi-site OMWaNA trial

in Uganda [33] and WHO-led multi-centre I-KMC trial [34]. We aim to align data definitions and maximise opportunities for pooled analyses with the OMWaNA trial.

The primary outcome results of the eKMC trial will contribute to the global evidence base for use of KMC before stabilisation in preterm neonates, with secondary outcome results and other analyses providing insights to how KMC is effective, particularly regarding infection prevention. The eKMC trial aims to inform one of the great divides between resource-limited and resource-rich settings and improve the chance for newborns everywhere to survive and thrive.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-020-4149-y.

Additional file 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents.

Additional file 2. aSCRIP definition.

Abbreviations

AE: Adverse events; aPSBI: Adapted possible severe bacterial infection; aSCRIP: Adapted stability of cardio-respiratory in preterm infants; CI: Confidence interval; CLSI: Clinical and Laboratory Standards Institute; CONS: Coagulase-negative staphylococcus; CPAP: Continuous positive airway pressure; CSF: Cerebral-spinal fluid; DSMB: Data safety monitoring board; EFSTH: Edward Francis Small Teaching Hospital; ESBL: Extended-spectrum beta lactamase; ISO: International Organisation for Standardisation; IV: Intravenous; KMC: Kangaroo mother care; LSHTM: London School of Hygiene & Tropical Medicine; MRCG: Medical Research Council Unit The Gambia at London School of Hygiene & Tropical Medicine; NMR: Neonatal mortality rate; PI: Principal investigator; RCT: Randomised controlled trial; RR: Risk ratio; SAE: Serious adverse event; SD: Standard deviation; SDGs: Sustainable development goals; TSC: Trial Steering Committee; VBA: Visual Basic Application; WHO: World Health Organisation

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Trial status

Recruitment began on 23 May 2018 and is expected to continue until June 2020.
Protocol date and version: V4.0, 18 March 2019
Revision chronology:
V1.2, 14 February 2018: Original protocol approved.
V2.1, 7 July 2018, Amendment 1 (substantial, made in response to internal pilot phase and recommendations from TSC and DSMB) and including a reduction in the secondary outcomes, adjustment in the definition of AE and SAEs to better reflect population of unstable neonates, randomisation blocks changed to not specify size of permuted blocks, strengthening of allocation procedures, window period of 5 days included for follow-up, blood and CSF samples transportation windows adjusted, SAE reporting period prolonged for non-fatal SAEs and DSMB reporting timelines changed to bi-monthly safety reports, stopping criteria expanded from 5 to 10 min in event of severe instability, and minor changes made to definitions of source documents and collection of data in electronic formats
V3.0, 4 Sept 2018, Amendment 2 (substantial, made in response to external changes to standard care at study site which impacted on stability definitions), including a change to the stability definition to include the use of bubble CPAP, a reduction in the intensity of the study assessments once participants become stable, removal of continuous temperature monitoring, removal of environmental temperature monitoring, and changes made in how the patient flow is recorded.
V4.0, 18 March 2019, Amendment 3 (non-substantial), including clarification of the definition of clinically suspected infection.

Trial sponsor

London School of Hygiene & Tropical Medicine (LSHTM)
Sponsors reference: QA1078
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The study sponsor and funder had no role in the study design, data collection, study management or planned analysis. They had no input into the writing of the report or decision to submit for publication and do not have any authority over any of the above activities. Participants will receive compensation for any harm suffered as a result of the trial as per the sponsor's standard indemnity.

Composition, roles and responsibilities of the trial team

Trial Steering Committee:
Professor Enitan Carrol, University of Liverpool (Chair); Professor Elizabeth Mason; Professor Chinyere Ezeaka; Dr. Jane Crawley; Dr. Baderinwa Abatan; Professor Diana Elbourne; Professor Simon Cousens; Professor Joy Lawn; Dr. Anna Roca; Dr. Helen Brotherton
Role: Overview of study design & conduct; receipt of DSMB reports and action as appropriate; publication & dissemination of results
Trial Management group:
Dr. Helen Brotherton, Dr. Anna Roca, Dr. Abdou Gai, Mr Bunja Kebbeh, Mr Alpha Jallow, Mr Yusupha Njie, Miss Binta Saidy, Mrs Saffiatou Darboe
Role: Responsible for organisation and day-to-day conduct of the study; maintenance of data-entry, cleaning and verification system; laboratory management and financial administration of the study
MRCG Trial Monitors team:
Vivat Thomas Njie, Gibbi Sey, Fatou Joof, Maxine Heffner
Role: Monitoring progress of the study against ICH-GCP standards
eKMC Data Safety & Monitoring Board:
Professor Pollyanna Hardy, University of Birmingham (chair); Dr. Christabel Enweronu-laryea; Dr. Martin Ota; Dr. Anne Segonds-Pichon. Terms of reference for the DSMB are available on request from the eKMC PI (HB, corresponding author).

Authors' contributions

HB and JEL conceived of the research question, obtained the funding from Wellcome Trust and designed the protocol with substantial input from SMAZ, SC, ACS, AR and CJT. The study protocol was implemented by HB, AR, AG and ALS. HB wrote the first version of the manuscript. All authors read and approved the final version of the manuscript.

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This work is funded by The Wellcome Trust (Ref. 200116/Z/15/Z) as a Research Training Fellowship to HB. The funders played no role in the trial design or conduct and will not contribute to the analysis or interpretation of the data. They did not contribute towards the writing of this manuscript.

Availability of data and materials

The final trial dataset will be available on requests made to the PI or institutional delegate. The results of this study will be published in an open access format in a peer-reviewed biomedical journal, in addition to the PI's doctoral thesis. The results will be disseminated at relevant international scientific forums and communicated to the World Health Organisation. The Gambian Government Ministry of Health and Social Welfare and other relevant local stakeholders and participant families will be directly informed of the study results.

Ethics approval and consent to participate

Ethical approval was obtained for the study protocol and informed consent documents from LSHTM Intervention Ethics Committee (Ref. 14545) and Gambian Government/MRCG Joint Ethics Committee (Ref. 1591). Any

substantial changes to the study protocol which may impact on the study conduct or patient safety will be submitted to the ethics committees, and after approval, the sponsor, trial registry, TSC and DSMB will be notified. Details of the consent procedures are outlined in the main manuscript.

Consent for publication

Consent for obtaining the photograph (Fig. 3) and for publication was obtained from the caregiver featured in the photograph, using the MRCG at LSHTM photographic consent form.

Competing interests

The authors declare that they have no competing interests. The funder (Wellcome Trust) played no role in the design of the trial or writing of the manuscript.

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Publisher's Note

Chapter 6 - Survival and clinical effects of early kangaroo mother care prior to stability (Article 3)

6.1. Scope of chapter

This chapter presents the results and brief discussion of the eKMC trial primary and secondary outcome findings, as published in Lancet's EClinicalMedicine peer-reviewed journal.

6.2. List of figures

6.3. List of tables

6.4. Supplementary material

Supplementary materials include the eKMC trial protocol (Annex A-6-1), the eKMC trial statistical analysis plan (Annex A-6-2) and additional tables and figure (Annex A-6-3), listed as:

eFigure 1: Overview of eligibility criteria, study procedures and key definitions for eKMC trial

eFigure 2: Duration (minutes) spent in kangaroo position, by allocation arm and day of enrolment

eTable 1: Additional baseline characteristics for intention-to-treat population

eTable 2: Adjusted analysis for eKMC primary and secondary outcomes, adjusted for twin status, admission weight and gestational age

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eTable 6: Concomitant treatments received by intention-to-treat population during hospitalisation

The eKMC trial was reported as per CONSORT reporting guidelines, with the CONSORT checklist included in Annex A-6-4.

6.5. Citation

Brotherton H, Gai A, Kebbeh B, Njie Y, Walker G, Muhammad AK, Darboe S, Jallow M, Ceesay B, Samateh AL, Tann CJ, Cousens S, Roca A, Lawn JE. **Impact of early kangaroo mother care versus standard care on survival of mild-moderately unstable neonates <2000 grams: A randomised controlled trial.** EClinicalMedicine. 2021;39: 101050. Doi.101016/j.eclinm.2021.101050

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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	1601409	**Title**	Dr
First Name(s)	Helen		
Surname/Family Name	Brotherton		
Thesis Title	Early Kangaroo Mother Care for mild-moderately unstable neonates <2000g in The Gambia		
Primary Supervisor	Joy Lawn		

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?	EClinicalMedicine as: Brotherton H, Gai A, Kebbeh B, Njie Y, Walker G, Muhammad AK, Darboe S, Jallow S, Ceesay B, Samateh AL, Tann CJ, Cousens S, Roca A, Lawn JE. Impact of early kangaroo nother care versus standard care on survival of mild-moderately unstable neonates <2000 grams: A randomised controlled trial. EClinMed 2021;30:101050. Doi.101016/j.eclinm.2021.101050		
When was the work published?	1 September 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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 team for trial implementation, delegating to A Gai, B Kebbeh and G Walker for management of the field team and to S Darboe, M Jallow and B Ceesay for laboratory procedures. I designed the data collection tools and electronic database jointly with Y Njie and gave oversight to the data collection and data cleaning activities. I liaised with the Ethics Committees, DSMB, TSC, local saftey monitor, trial monitors and sponsor, providing written reports and arranging meetings as needed. I conducted the analysis with input from S Cousens and AK Muhammad. I interpreted the data with input from Joy Lawn, Anna Roca, Cally Tann and Simon Cousens. I wrote the manuscript, with input from Joy Lawn and incorporated feedback from co-authors. I co-ordinated submission and response to peer-reviewers comments.

SECTION E

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Date	25th Jan 2021

Supervisor Signature	Joy Lawn
Date	30th Jan 2021

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Research Paper

Impact of early kangaroo mother care versus standard care on survival of mild-moderately unstable neonates <2000 grams: A randomised controlled trial

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ABSTRACT

Background: Understanding the effect of early kangaroo mother care on survival of mild-moderately unstable neonates <2000 g is a high-priority evidence gap for small and sick newborn care.
Methods: This non-blinded pragmatic randomised clinical trial was conducted at the only teaching hospital in The Gambia. Eligibility criteria included weight <2000g and age 1–24 h with exclusion if stable or severely unstable. Neonates were randomly assigned to receive either standard care, including KMC once stable at >24 h after admission (control) versus KMC initiated <24 h after admission (intervention). Randomisation was stratified by weight with twins in the same arm. The primary outcome was all-cause mortality at 28 postnatal days, assessed by intention to treat analysis. Secondary outcomes included: time to death; hypothermia and stability at 24 h; breastfeeding at discharge; infections; weight gain at 28d and admission duration. The trial was prospectively registered at www.clinicaltrials.gov (NCT03555981).
Findings: Recruitment occurred from 23rd May 2018 to 19th March 2020. Among 1,107 neonates screened for participation 279 were randomly assigned, 139 (42% male [*n* = 59]) to standard care and 138 (43% male [*n* = 59]) to the intervention with two participants lost to follow up and no withdrawals. The proportion dying within 28d was 24% (34/139, control) vs. 21% (29/138, intervention) (risk ratio 0·84, 95% CI 0·55 – 1·29, *p* = 0·423). There were no between-arm differences for secondary outcomes or serious adverse events (28/139 (20%) for control and 30/139 (22%) for intervention, none related). One-third of intervention neonates reverted to standard care for clinical reasons.
Interpretation: The trial had low power due to halving of baseline neonatal mortality, highlighting the importance of implementing existing small and sick newborn care interventions. Further mortality effect and safety data are needed from varying low and middle-income neonatal unit contexts before changing global guidelines.

Abbreviations: aPSBI, (adapted Possible Severe Bacterial Infection); aSCRIP, (adapted Stability of Cardio-respiratory in Preterm infants); bCPAP, (bubble Continuous Positive Airway Pressure); CFR, (Case-fatality rate); CI, (confidence interval); CLSI, (Clinical & Laboratory Standards Institute); CONSORT, (Consolidated Standards of Reporting Trials); CSF, (Cerebral-Spinal Fluid); DSMB, (Data Safety Monitoring Board); eKMC trial, (early Kangaroo Mother Care before Stabilisation trial); EFSTH, (Edward Francis Small Teaching Hospital); GEE, (Generalized Estimating Equation); HR, (Hazard Ratio); ICH-GCP, (International Conference on Harmonisation – Good Clinical Practice); IQR, (Inter Quartile Range); IV, (intravenous); ISO, (International organisation for standardisation); KMC, (Kangaroo mother care); LMIC, (Low and middle-income countries); LSHTM, (London School of Hygiene & Tropical Medicine); MRCG, (Medical Research Council Unit The Gambia at London School of Hygiene & Tropical Medicine); MDR, (Multi-drug resistant); NA, (not applicable); NNU, (Neonatal Unit); RCT, (Randomised controlled trial); RD, (Risk difference); RDS, (Respiratory Distress Syndrome); RR, (Risk Ratio); SAE, (Serious Adverse Event); SD, (Standard Deviation); SDG, (Sustainable Development Goal); SSA, (Sub-Saharan Africa); WHO, (World Health Organisation)

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Research in context

Evidence before this study

Kangaroo mother care (KMC) is recommended by the World Health Organization (WHO) for all stable neonates ≤2000 g with the latest Cochrane review (2016) reporting 40% relative reduction in mortality at discharge or 40 – 41 weeks' post-menstrual age, compared to standard incubator care (RR=0·60, 95% CI 0·39 – 0·92; 8 trials; 1736 neonates). This Cochrane review highlighted insufficient evidence to recommend early-onset continuous KMC before stabilisation, and recommended methodologically rigorous trials to determine the effectiveness of KMC in "unstabilised or relatively stabilised low-birth weight infants". We searched clinicaltrials.gov and the Australian New Zealand Clinical Trials Register with the search terms "kangaroo", "kangaroo mother care", "kangaroo method" or "skin to skin contact AND neonate", and identified two other trials currently ongoing or recently closed which also address this priority question (OMWaNA; clinicaltrials.gov NCT02811432 and WHO's iKMC trial; ACTRN12618001880235).

Added value of this study

This pragmatic, individually randomised controlled trial (n = 279) conducted at a Gambian level 2+ neonatal unit did not find evidence of improved survival at 28 postnatal days with early KMC versus standard care for mild-moderately unstable neonates <2000 g. Halving of inpatient case-fatality rates (48% pre-trial vs. 23% during-trial) contributed to reduced power to detect a difference in the primary outcome. There was no evidence of between-arm differences for secondary outcomes or serious adverse events however one-third of intervention neonates reverted to standard care for clinical reasons. Achieving prolonged KMC duration was challenging with barriers including absence of willing KMC providers, provision to twin pairs and need for a respectful neonatal unit environment.

Implications of all the available evidence

Implementation of early KMC for vulnerable unstable newborns is challenging, and studies are required in a range of neonatal care settings before this can be recommended as standard care. Implementation research is needed from perspectives of the mother/family, healthcare provider as well as health systems planning and costings data, with understanding of the KMC dose-response by risk profile a priority evidence gap. Although this trial did not show a mortality effect, findings can contribute to future meta-analyses, and demonstrate potential for substantial survival gains through improved quality small and sick newborn care.

1. Introduction

An estimated 15 million neonates are born preterm (<37 weeks gestation) annually, over 80% in Asia and Sub-Saharan Africa (SSA) [1]. Complications of preterm birth result in >1 million neonatal deaths/year [2] with the highest risk of death during the first 24 h after delivery [3]. Birth weight <2000 g is a proxy for prematurity yet this group of vulnerable neonates may also include term neonates who are small for gestational age (SGA) as well as preterm neonates with or without growth restriction. Mortality risk is greatest for preterm neonates who are also SGA [4] and all neonates <2000 g require high quality small and sick newborn care especially during the first day after birth. There is an urgent need for evidence-based interventions for neonates <2000 g in order to meet the Sustainable Development Goal 3.2 target of ≤12 neonatal deaths/1000 live births by 2030 [5].

Kangaroo mother care (KMC) is recommended as standard care for all stable neonates ≤2000 g [6]. KMC is an evidence based package of care, with key component of prolonged skin-to-skin contact between neonate and caregiver [6]. This is linked to promotion of exclusive breastmilk feeding and early hospital discharge [7]. Compared to incubator care, KMC is associated with a 36–51% reduction in mortality at discharge or at 40–41 weeks postmenstrual age [7–9]. There is a lack of evidence for KMC in "relatively stable or unstable" neonates [9], hence it is not currently recommended by WHO for this population [6]. This evidence-gap is a high priority [9] with several on-going or recently completed trials in SSA and South Asia [10,11].

If shown to be effective and safe, early KMC may result in a paradigm shift in hospital care of small and sick neonates, both improving outcomes and promoting family-centred care. eKMC was intended to be a pragmatic trial, aiming to assess the effect of early KMC on 28-day survival of mild-moderately unstable neonates following neonatal unit admission. As secondary objectives, we explored potential ways by which early KMC may alter preterm outcomes such as thermal control [12]; cardio-respiratory stabilisation [13]; promotion of breastfeeding [14] and avoidance of infections [9]. Secondary objectives also included safety evaluation, for which there is limited data from low and middle-income countries (LMIC).

2. Methods

2.1. Design & setting

An individually randomised superiority trial was conducted at Edward Francis Small Teaching Hospital (EFSTH), the only teaching hospital and referral Neonatal Unit (NNU) in The Gambia. Twelve percent of Gambian neonates are born preterm [1] and 29% of neonatal deaths at EFSTH are due to complications of prematurity [15] with 48% case fatality for neonates <2000 g [16]. Special newborn care (WHO Level 2+) [16] was available with oxygen via concentrators, phototherapy, pulse-oximetry for spot-checks, intravenous (IV) fluids via burettes and gastric tube feeding. Bubble CPAP (bCPAP) was introduced to the NNU in early 2018, but only became embedded in small and sick newborn care around the time of trial onset. Mechanical ventilation, surfactant, blood pressure measurement, continuous pulse oximetry monitoring and parenteral nutrition were unavailable. Running water was intermittently available, with water buckets and soap for maternal hand washing and no access to an autoclave for sterilisation of re-usable equipment. Two nurses per shift cared for up-to 80 neonates during peak periods. Continuous KMC was established as standard of care for stable neonates ≤2000 g in September 2017, provided on an eight-bed KMC unit adjacent to the NNU. An area within the NNU was identified as the "trial area", where both control and intervention arm participants were managed.

2.2. Participants, screening & consent

All admitted singleton or twin neonates weighing <2000 g and aged 1–24 h were screened for exclusion criteria, including: recruitment to another research study; triplets; major congenital malformations; severe jaundice; seizures; stable or severely unstable; absence of study bed and lack of written informed consent within 24 h of admission (Fig.S1). Presence of mother or another caregiver who was willing to provide the intervention was also required. Our target population was mild-moderately unstable neonates with severely unstable newborns excluded due to the operational challenges of providing KMC alongside resuscitation and bCPAP in our setting [17]. Stable neonates were excluded as they should already receive KMC.

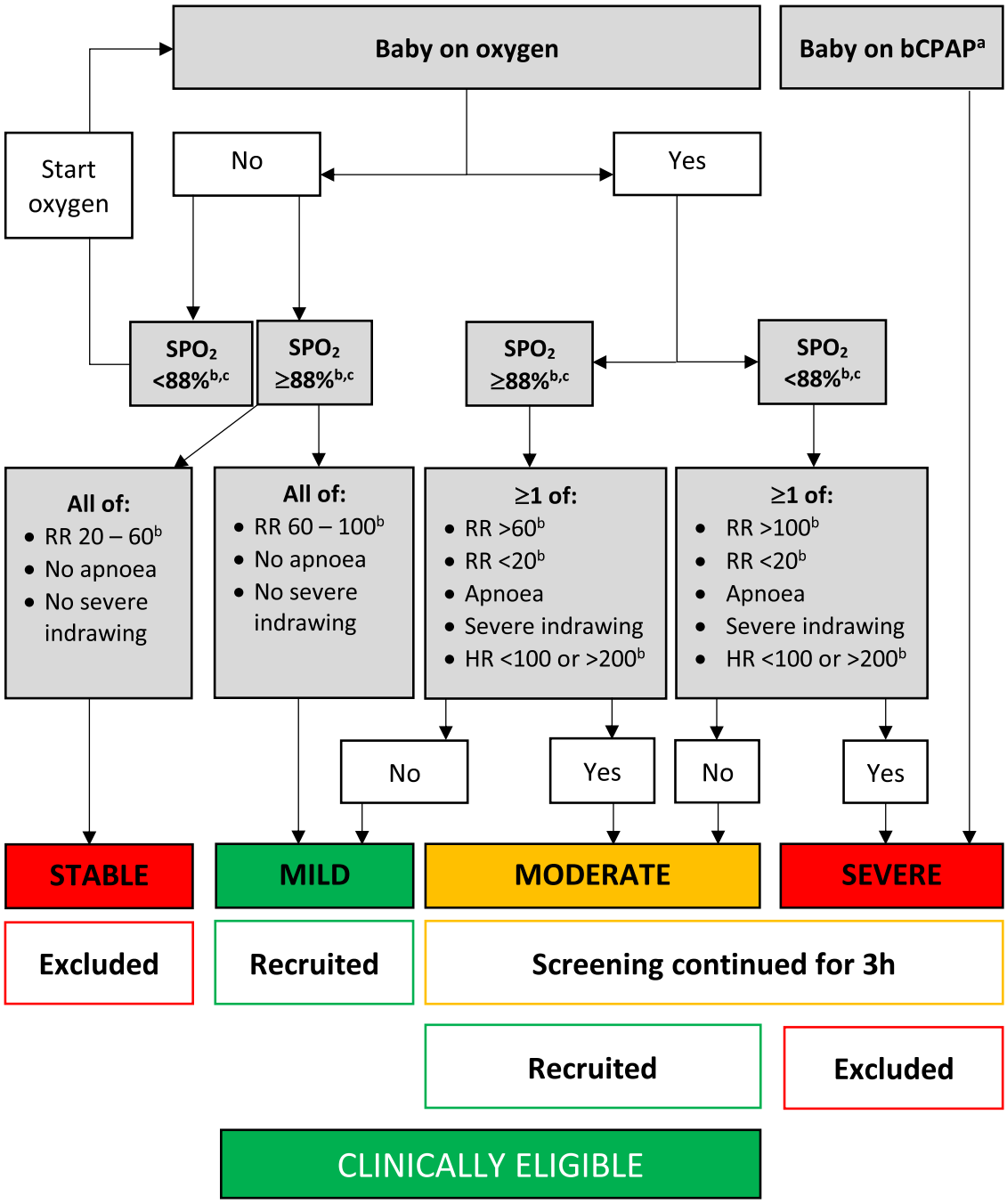

Fig. 1. Definitions of stability used in eKMC trial. Originally published by BMC [18]. a. Criteria for starting bCPAP were: Silverman-Anderson score ≥4 with no apnoea and/or heart rate <100 bpm. b. SPO_2, respiratory rate and heart rate were recorded every minute for a 10 min period and classified according to most frequent category of observations present for >5 min. c. Upper limit of SPO_2 for providing oxygen therapy was 95%. Abbreviations: bCPAP= Bubble continuous positive airway pressure; RR=Respiratory rate; *h*=hours; HR=Heart rate; SPO_2=oxygen saturation.

In the absence of validated stability scores suitable for non-intensive care settings [18], we developed pragmatic stability definitions based on clinical and cardio-respiratory observations feasible for low-resource settings, namely respiratory rate, heart rate, oxygen saturation and work of breathing (Fig. 1). Thresholds for abnormality were chosen for consistency with WHO recommended references ranges [19], with a lower oxygen saturation threshold (<88%) to avoid over classification of severe instability. Cardio-respiratory stability was assessed in potentially eligible neonates over 10 min with a Nonin™ 2500A pulse oximeter. Mildly unstable neonates were immediately recruited. Moderately and severely unstable neonates underwent repeat assessment after 3 h with exclusion of severely unstable neonates at this stage. Written informed consent was sought from the first caregiver on-site within 24 h of admission. The parent was preferred consenter but other relatives could consent with later parental assent/consent to continue participation. If consent was provided at >3 h since the last stability assessment, stability status was re-checked to avoid recruitment of neonates out-with the stability definition.

2.3. Randomisation, allocation and blinding

The unit of randomisation was the mother with stratification by the neonate's admission weight (<1200 g/ ≥1200 g; cut-off chosen to

identify highest risk neonates). If both babies in a twin set were eligible, they were randomised to the same arm for convenience of care, according to the first eligible twins' weight. Random permuted blocks of varying size were used and randomisation sequence was computer generated by an independent statistician. Selection bias was avoided by using sequentially numbered, opaque sealed envelopes, opened by research nurse after baseline assessment and time-stamped to identify any subversion of sequence. Due to the nature of the intervention, blinding of intervention procedures and outcome assessments wasn't possible but laboratory processes (for confirmed infections) and analyses were blinded to allocation.

2.4. Intervention

We defined KMC as skin-to-skin contact in the kangaroo position, with the naked (except for hat and diaper) neonate laying prone next to the caregivers' chest in a frog-leg position with head turned sideways. A cloth wrapper [Thari design] was used to secure the neonate in KMC position, including straps tied at the sides of the infant to enable easy access [17]. Research nurses encouraged the KMC provider to start KMC immediately after allocation and to provide as close to continuous skin-to-skin contact as possible [6], aiming for >18 h/day in prolonged sessions. Beds were provided on the NNU for the exclusive use of the intervention arm caregivers. All other treatments were provided simultaneously with KMC, except for bCPAP which was provided in the high dependency area of the NNU where it was not feasible to have adult KMC beds. During breaks to pray, wash, eat etc., the neonate was placed on a non-servo controlled radiant heater or incubator in the same room. Twins received KMC from the same or different KMC providers. Clinical criteria for stopping KMC were pre-specified and included: severe instability, including need for bCPAP; apnoea needing resuscitation; widespread rash on neonate or KMC provider; severe abdominal distension; omphalitis; phototherapy; blood transfusion; seizures, and KMC provider unwilling or unavailable to provide continuous KMC. Criteria for re-starting KMC were also pre-specified (eFig.1) [17]. Neonates were transferred to the KMC unit to continue KMC once stability criteria were met and neonates tolerated enteral feeds without IV fluids for 12 h.

2.5. Control

Control neonates were managed in an incubator or under a radiant heater (non-servo controlled) in the same room as intervention neonates. The caregiver could touch and feed but KMC was not permitted until the neonate met stability criteria at >24 h after admission (Fig.1). Intermittent KMC (minimum 60 min skin-to-skin contact several times a day) was provided whilst the neonate was still on the neonatal unit, with continuous KMC starting after transfer to the KMC unit once stability criteria were met and neonates tolerated enteral feeds without IV fluids for 12 h.

2.6. Outcome measures

The primary outcome was all-cause mortality at 28 days. Secondary outcomes included: time to death; stability at 24 h, using the Stability of Cardio-Respiratory in Preterm Infants (SCRIP) score [20], modified for relevance to neonates receiving oxygen [17]; prevalence of hypothermia (axillary temperature <36·5 °C) at 24 h; proportion exclusively breastfeeding at discharge; mean daily weight gain at 28 +/−5d; incidence of clinically suspected infection from age 3 to 28 days or latest follow-up, and mean duration of admission.

2.7. Trial procedures, including safety assessments

A detailed description of trial procedures is available in the published protocol (efig.1) [18].

To avoid preferential education of caregivers in the intervention arm, the first caregiver available on the NNU for both groups was sensitised about NNU policies, KMC provision, hand hygiene and danger signs.

Continuous pulse-oximetry monitoring was performed for trial participants during the first 24 h and continued until the neonate was stable off oxygen. Heart rate, oxygen saturation (SPO_2), respiratory rate, blood glucose, axillary temperature, stability status, and adverse events were recorded six-hourly for the first 24 h then daily whilst on the neonatal unit. Following transfer to the KMC unit, study assessments were done on postnatal days 7, 14, 21, 28, with daily vital sign checks by EFSTH team as per standard care. Weight was measured daily from postnatal day five and length/head circumference weekly. A clinician examined participants within 24 h of enrolment and evaluated gestational age with the New Ballard score within 48 h [21].

The WHO's Possible Serious Bacterial Infection (PSBI) criteria were used to identify clinical deterioration with adaptations to increase relevance for hospitalised preterm infants by including excessive gastric aspirates, need for oxygen or bCPAP and breathing rate >80 bpm (efig.1) [17]. If ≥1 aPSBI criteria was present, neonates were assessed by a clinician for infection, which was diagnosed as per a validated nosocomial risk score for preterm neonates (age >72 h with ≥1 of apnoea, lethargy, pallor, jaundice, or hepatomegaly) [22]. Peripheral blood and CSF (if no contra-indication present) samples for culture were obtained under aseptic technique by trained clinicians if infection criteria were met (efig.1). Confirmed infection was diagnosed if suspected infection criteria were present and a known neonatal pathogen was isolated. Coagulase negative staphylococcus and bacillus species were pre-defined as non-pathogenic in this population due to the absence of indwelling catheters and lines.

Research nurses directly observed and recorded duration spent in kangaroo position for both arms, documenting timing of each KMC session, KMC provider and reason for coming out of KMC position. All other treatments were provided by EFSTH personnel according to standardised guidelines consistent with standard care and WHO recommendations for small and sick newborn care [6,19], with compliance monitored daily by trained clinicians to avoid performance bias. Guidelines included hospital discharge criteria: minimum weight 1.1 kg; >10 g/kg/day weight gain for 3 consecutive days without gastric tube feeding; both twins met weight criteria; stable vital signs and no health worker concerns; mother willing to continue KMC at home and able to attend follow-up [17]. The final study visit at postnatal age 28+/−5d was by inpatient review if admitted or scheduled follow-up at the site with re-imbursement of travel expenses and home visits for participants who did not attend.

All data were collected by Good Clinical Practice (ICH-GCP) trained personnel with three to six monthly re-training on study specific procedures. The REDCap™ electronic data entry system was used with built-in consistency checks. Double-blind standardisation assessments for gestational age and anthropometric measurements were performed to reduce inter-observer variability. Triplicate measurements of temperature and anthropometric data were obtained and cardio-respiratory parameters were measured over ten minutes to generate mean values. Calibrated equipment was used for all measurements including Seca 757 digital weighing scale (2 g gradation) and glucometers for bedside blood glucose monitoring.

2.8. Microbiological procedures

Blood cultures were processed within 24 h in a BACTEC 9050 BD at the MRC Unit The Gambia at LSHTM (MRCG) laboratory (ISO15189 accredited) with sub-culture by conventional methods including species identification using the API-20 system and antibiotic susceptibility testing by disc diffusion according to the Clinical and Laboratory Standards Institute (CLSI) 2018 guidelines.

2.9. Sample size calculation and statistical analysis

A sample size of 392 neonates (196 per arm) was chosen to provide 80% power to detect a 30% relative difference (48% vs. 34%) in mortality with a type I error rate of 5%. The baseline mortality rate of 48% was estimated from feasibility study data (56%, 14/25, in-patient case fatality rate for neonates meeting trial definitions of mild-moderate instability) assuming a 15% relative reduction related to trial implementation and was consistent with published pre-trial data [15].

Analyses were done using STATAv.16 with an intention-to-treat approach, using techniques to account for twin clustering. Between-arm differences in categorical outcomes were analysed using a generalised estimating equation (GEE) model with log link and an independent working correlation structure. A random effects model was used for continuous outcomes. Cox regression with frailty was used for time to death with right censoring of data for participants not followed up. The primary analysis was unadjusted for covariates with pre-planned analyses adjusting for twin status, weight, and gestational age. A pre-planned sub-group analysis of all outcomes was performed for weight and twin pregnancy status with an interaction term to assess for heterogeneity of treatment effects across subgroups. All tests were two-sided and reported without adjustment for multiple testing. Missing data was low (<5%), hence complete case analysis was used.

An unblinded interim analysis was conducted by the data safety monitoring board (DSMB) after randomisation of 50% of the target sample size (n = 196). In March 2020 the Trial Steering Committee recommended stopping recruitment early (~70% of target sample size recruited) as the trial was recognised to now be underpowered due to reductions in baseline mortality and the COVID-19 pandemic posed an immediate risk to staff health.

2.10. Ethics

Approval was received from the institutional review board at LSHTM and the Gambian Government / MRCG Joint Ethics Committee. This article was prepared in accordance with CONSORT guidelines (Online-only material 1) [23].

2.11. Role of the funding source

The funder played no role in study design, data collection, analysis or interpretation of data, manuscript writing nor decision to submit for publication.

3. Results

Recruitment spanned from 23rd May 2018 to 19th March 2020 with follow-up completed by 20th April 2020. 1107 newborns were screened and 279 (25%) met eligibility criteria; 141 were allocated to receive standard care and 138 to early KMC. Among the main reasons for non-recruitment were severe instability or death during the screening process (217/1107, 19.6%), unavailability of a willing KMC provider during the first 24 h of NNU admission (168/1107, 15.2%) and limited availability of trial beds on the NNU (77/1107, 7%). There were no withdrawals and only two neonates were lost to follow-up. 277 neonates were included in the analysis of the primary outcome (Fig.2).

Our cohort consisted of mostly premature neonates (median gestational age 32 weeks in control, 33 weeks in intervention), with median admission weight <1.5 kg in both arms (1436 g control; 1459 g intervention) (Table 1). Nearly one-third (32% control vs 30% intervention) of participants were part of a twin pregnancy and 17% (both arms) of the cohort were twins with both enroled. Most

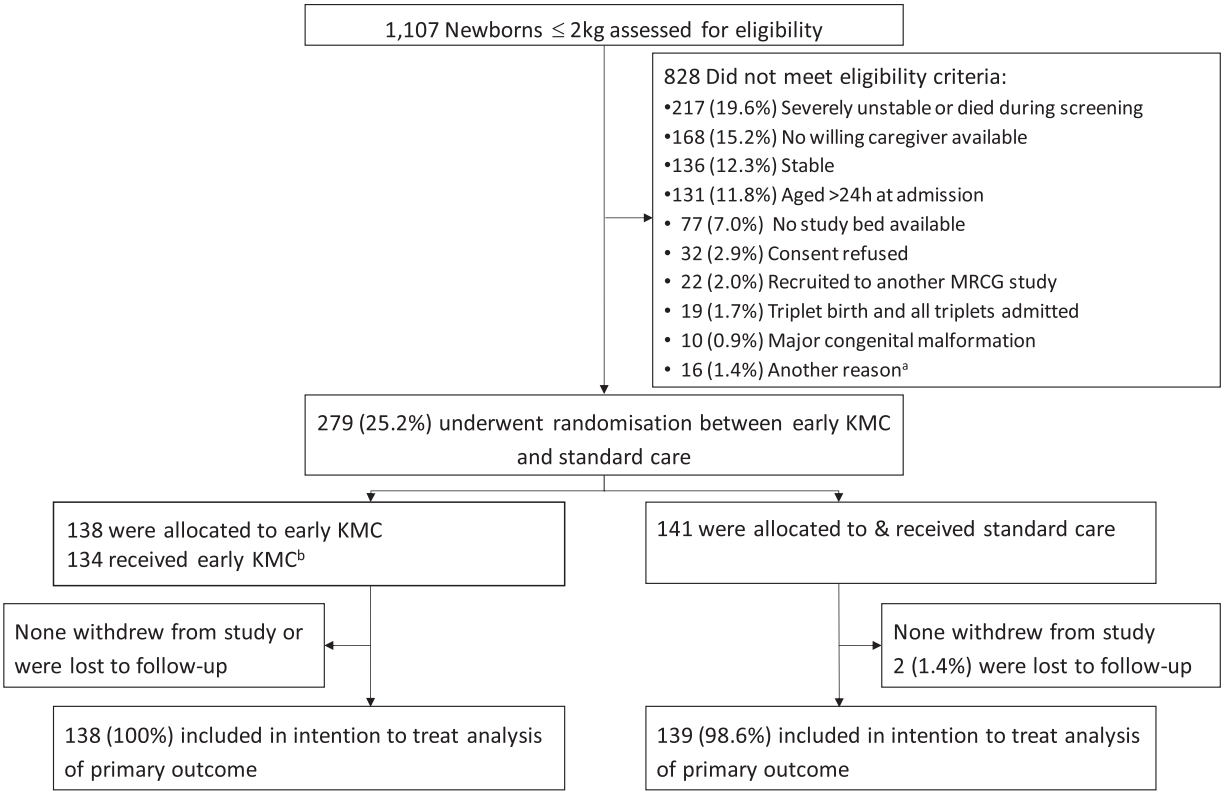

Fig. 2. Overview of enrolment, randomisation & inclusion in intention to treat analysis of primary outcome. a. Other reasons for non-recruitment were weight ≥2000 g on trial scales (6); planned team retraining (5); seizures (3); political protests leading to temporary halt to recruitment (1) and not known (1). b. Reasons for not receiving early KMC in the intervention arm were clinical deterioration between screening and start of intervention procedures (2); no study bed available (1); no caregiver available (1). Abbreviations: *h*=hours; KMC = Kangaroo mother care.

Table 1
Baseline characteristics of the intention-to-treat population.

	Standard care (*N* = 141)	early KMC (*N* = 138)
Neonatal & perinatal characteristics		
Male sex, N° (%)	59 (42)	59 (43)
Age at admission (h), median (IQR)	2·3 (0·7 – 5)	2·3 (0·9 – 4·7)
Age at start of intervention/control[a] (h), median (IQR)	12·8 (7·9 – 19·1)	13·6 (8·9 – 19)
Admission weight (g), median (IQR)	1436 (1180 - 1660)	1459 (1204 – 1650)
Distribution of admission weight,[b] N° (%)		
<1200 g	39 (28)	34 (25)
≥1200 g	102 (72)	104 (75)
Part of twin gestation pregnancy, N° (%)	45 (32)	41 (30)
Part of twin pregnancy, both enroled, N° (%)	24 (17)	24 (17)
Gestational age (weeks), median (IQR) (*n* = 271)	32 (31 - 34)	33 (31 - 34)
Distribution of gestational age, N° (%)		
<28 weeks	4/135 (3)	3/136 (2)
28 – 31+6 weeks	36/135 (27)	41/136 (30)
32 – 36+6 weeks	83/135 (61)	81/136 (60)
≥37 weeks	12/135 (9)	11/136 (8)
Referral-site (EFSTH), N° (%)	66 (47)	66 (48)
Health facility delivery, N° (%)	121 (86)	126 (91)
Caesarean-section delivery, N° (%)	27 (19)	31 (22)
Resuscitation at delivery,[c] N° (%)	10/140 (7)	5 (4)
Perinatal septic risk factors,[d] N° (%)	49/139 (35)	40/137 (29)
Neonatal stability & management at start of intervention/control procedures		
Stability status,[e] N° (%)		
Stable[f]	5 (4)	14 (10)
Mildly unstable	86 (61)	73 (53)
Moderately unstable	44 (31)	44 (32)
Severely unstable[f]	5 (4)	2 (1)
Axillary temperature (°C), median (IQR)(*n* = 277)	36·6 (36·1 – 37·2)	36·6 (36·1 – 37·1)
Blood glucose (mmol/L), median (IQR)(*n* = 275)	4·1 (3·5 – 5·1)	3·8 (3·2 – 4·9)
Oxygen saturation (SPO_2), median (IQR)(*n* = 274)	97 (96 - 98)	97 (95 - 98)
Oxygen, N° (%)	125 (89)	123 (89)
Bubble CPAP, N° (%)	5 (4)	2 (1)
IV antibiotics,[g] N° (%)	123 (87)	124/137 (91)
IV maintenance fluids, N° (%)	125 (89)	115 (83)
IV vitamin K prophylaxis, N° (%)	117 (83)	111 (80)
Apnoea of prematurity prophylaxis (IV caffeine or aminophylline), N° (%)	74 (52)	57(41)

a. The start of intervention/control procedures was defined as when a trial pulse oximeter was attached to the neonate, immediately after allocation yet prior to any intervention procedures commencing.
b. Categories of admission weights as per weight cut offs used for stratification during randomisation.
c. Resuscitation at delivery with one or more of: oxygen, bag-valve-mask ventilation or chest compressions.
d. Perinatal septic risk factors included: maternal fever; maternal chorioamnionitis; offensive smelling liquor; prolonged rupture of membranes >18 h.
e. Stability definitions as per published protocol[18] and as shown in Fig. 1.
f. Stable and severely unstable neonates were excluded during the screening phase but some eligible neonates improved or deteriorated during the consent and recruitment process, hence were stable or severely unstable when re-assessed at the start of intervention/control procedures.
g. Blood cultures were not obtained prior to antibiotic administration as they were not routinely available as part of standard care at the trial site.
Abbreviations: CPAP = Continuous positive airway pressure; EFSTH= Edward Francis Small Teaching Hospital; *g*=grams; *h* = hours; IQR = Interquartile range; IV = Intravenous; SD = standard deviation; SPO_2 = oxygen saturation.

neonates received oxygen therapy (89% both arms), antibiotics (87% vs. 91%) and intravenous fluids (89% vs. 83%) before allocation. 92% (control) vs. 88% (intervention) were mild or moderately unstable at the start of intervention/control procedures, with the remainder either improving or deteriorating between the end of screening and start of study procedures. There were two clinically relevant imbalances between treatment arms: (1) More neonates in the intervention arm were stable at the start of intervention/control procedures (2) Fewer neonates in the intervention arm received apnoea of prematurity prophylaxis before allocation. Baseline characteristics were otherwise balanced between arms (Table 1, eTable 1).

There was no evidence of a difference in mortality between arms in the primary intention-to-treat analysis, with 34/139 (24%) deaths in the control group versus 29/138 (21%) deaths in the intervention group (RR=0·84, 95% CI 0·55 – 1·29, Table 2) or with the survival analysis (Fig.3). Adjustment for admission weight, gestational age and twin status yielded similar results (RR=0·93, 95% CI 0·63 – 1·36, eTable 2). A sensitivity analysis excluding neonates not meeting eligibility criteria at the start of intervention/control procedures showed no evidence of between-arm effect difference (28/129 in control vs. 28/124 in intervention. RR=1·04, 95% CI 0·65 – 1·65, eTable 3).

There was no evidence of between-arm differences in secondary outcomes, including clinically suspected infections which were relatively common (15% (21/141) of control arm versus 20% (28/138) of intervention arm. RR=1·36, 95% CI 0·81 – 2·28) and blood culture confirmed infections (RR=1·53, 95% CI 0·65– 3·64, Table 2). The ten confirmed infections were all due to gram-negative bacteria with 82% (9/11) of isolates resistant to both 3rd generation cephalosporins and gentamicin (eTable 4).

Pre-planned sub-group analyses found no evidence of between-arm differences in outcomes except for admission weight. Among neonates <1200 g, early KMC was associated with a reduction in hypothermia at 24 h (RR=0·55, 95% CI 0·33 – 0·91) with no association apparent in neonates ≥1200 g (RR= 1·29, 95% CI 0·87 – 1·91; test of interaction $p = 0·008$) (Table 3).

21% (58/279) of participants experienced at least one clinically relevant non-fatal serious adverse event (SAE), most commonly a life threatening condition or a condition with high risk of disability

Table 2
Effect of early KMC on primary and secondary outcomes.

	Standard care	Early KMC	Effect estimate *(95% CI)*	*P* value
All-cause mortality at 28 days, N°(%)	34/139 (24)	29/138 (21)	RR= 0.84 *(0·55 – 1·29)*	0·423
Time to death (h), median (IQR)	*N* = 139 34 deaths 98·5 (29 – 132)	*N* = 138 29 deaths 90 (65 – 172)	HR= 0·83 *(0·50 – 1·35)*	0·447
aSCRIP score at 24 h of enrolment, median, (IQR)	*N* = 135 5 (4 – 6)	*N* = 134 5 (4 – 5)	MD −0·05 *(−0·25 – 0·16)*	0·667
Hypothermia (*T*<36·5 °C) at 24 h of enrolment, N° (%)	55/135 (40)	51/134 (38)	RR= 0·93 *(0·69 – 1·26)*	0·654
Exclusive breastfeeding[a] at discharge, N° (%)	105/107 (98)	107/109 (98)	RR= 1.0 *(0·96 – 1·04)*	0·985
Clinically suspected infection from 3 – 28 days, N° (%)[b]	21/141 (15)	28/138 (20)	RR= 1·36 *(0·81 – 2·28)*	0·240
Blood culture confirmed infection[c,d] from 3 – 28 days, N° (%)	4/141 (3)	6/138 (4)	RR= 1·53 *(0·65– 3·64)*	0·333
Duration of admission (days), mean (SD)	*N* = 106 16·3 (10·0)	*N* = 108 16·6 (11·1)	MD +0.3 *(−60·5 – 75·1)*	0·833
Weight gain at 28d (g/day), mean (SD)	*N* = 101 12·5 (12·1)	*N* = 103 10·3 (10·1)	MD −2·2 *(−5·28 – 0·81)*	0·150

Exclusively breastfeeding defined as only receiving breastmilk and no formula milk supplementation.
Defined as neonates with at least 1 suspected infection, as per protocol definition.[18] Two neonates (one in each allocation arm) each had two discrete infection episodes.
Blood cultures were obtained from 92% (47/51) of suspected late-onset infection episodes; 95% (21/22) from control arm and 90% (26/29) from intervention arm. 21% (10/47) of blood cultures were positive with 6% (3/47) presumed contaminated samples (coagulase negative staphylococcus isolated) and no between-arm difference in mean blood volume sampled (1.1 ml (SD 0.3) in control arm versus 1.0 ml (SD 0.3) in intervention arm, $p = 0.238$, student t-test).
CSF samples were obtained from 19 neonates meeting infection criteria and all were negative after 48 h culture.
Abbreviations: CI = confidence intervals; *h* = hours; HR = Hazard ratio; IQR = Interquartile range; KMC = kangaroo mother care; MD = mean/median difference in intervention arm; RR= risk ratio; SD = standard deviation.

(eTable 5). All SAEs were judged to be unrelated to the intervention with no between-arm differences. One third (46/138) of participants receiving early KMC met criteria to stop, at a median of 3·7d (IQR 1·6 – 6·2d), most commonly due to severe instability (16/46, 35%), isolated apnoea needing resuscitation (10/46, 22%) or needing phototherapy (8/46, 17%) (Table 4).

99% (136/138) of neonates in the intervention arm received KMC with 86% (119/138) starting KMC within 24 h of admission (median

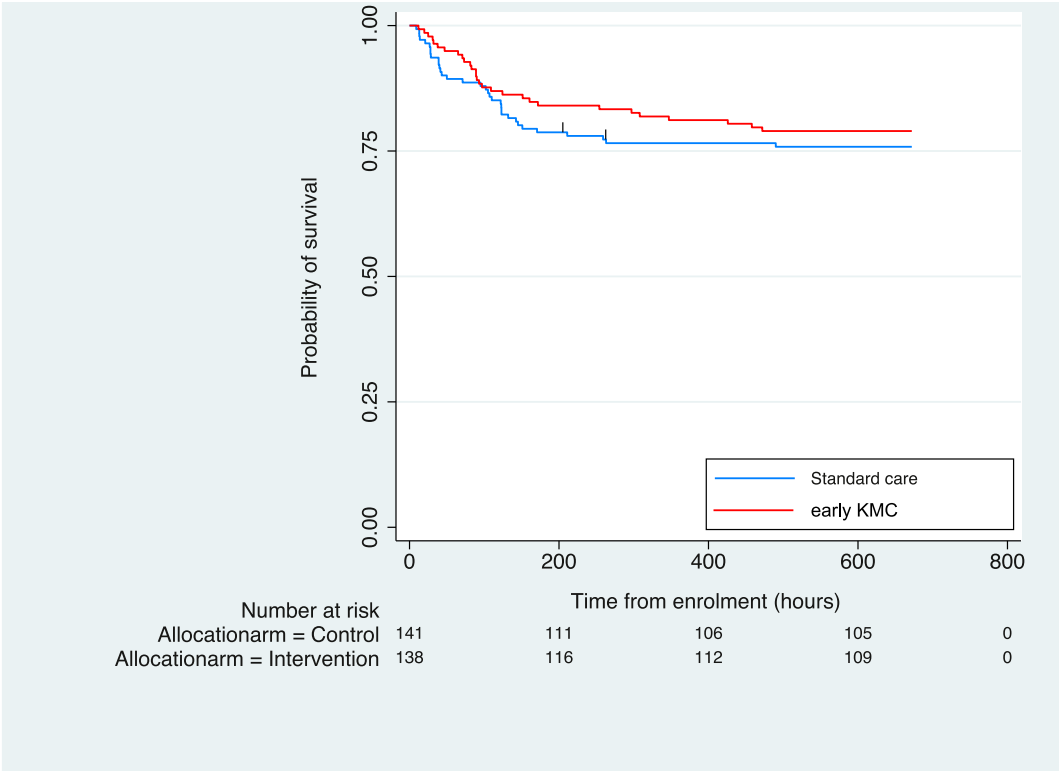

Fig. 3. Cumulative incidence of survival over time from start of intervention/control procedures.

Table 3
Sub-group analysis of eKMC trial outcomes, by admission weight and twin status.

	Subgroup	Nº / Total Nº (%) Standard care (n = 139)	Early KMC (n = 138)	Effect size (95% CI); P for effect of intervention within each sub-group stratum	P value for test for interaction between treatment arms and sub-group strata
All-cause mortality at 28 days, Nº (%)	Admission weight <1200 g	19/37 (51)	14/31 (45)	RR 0·88 (0·53 – 1·45); *0·614*	0·849
	Admission weight ≥1200 g	15/102 (15)	15/107 (14)	RR 0·95 (0·49 – 1·85); *0·888*	
	Singleton	25/94 (27)	21/97 (22)	RR 0·98 (0·42 – 2·29); *0·955*	0·721
	Twin pregnancy	9/45 (20)	8/41 (20)	RR 0·81 (0·49 – 1·35); *0·426*	
Time to death, (h), median	Admission weight <1200 g (n = 19; n = 14)	95	82	HR: 0·86 (0·43 – 1·71); *0·665*	0·888
	Admission weight ≥1200 g (n = 15; n = 15)	107	151	HR: 0·92 (0·45 – 1·89); *0·825*	
	Singleton (n = 25; n = 21)	71	109	HR: 0·75 (0·42 – 1·34); *0·334*	0·593
	Twin pregnancy (N = 9; n = 8)	123	76	HR 1.02 (0.39 – 2.64); *0.970*	
aSCRIP score at 24 h, mean	Admission weight <1200 g (n = 36; n = 28)	4·6	4·6	MD 0 (−0·36 – 0·48); *0·780*	0·490
	Admission weight ≥1200 g (n = 99; n = 106)	5·1	5·0	MD −0·1 (−0·34 – 0·12); *0·358*	
	Singleton (n = 90; n = 94)	4·9	4·9	MD 0 (−0·24 – 0·25); *0·970*	0·509
	Twin pregnancy (n = 45; n = 40)	5·0	4·9	MD −0·1 (−0·51 – 0·22); *0·440*	
Hypothermia (T<36·5 °C) at 24 h, Nº (%)	Admission weight <1200 g	25/36 (691)	11/28 (39)	RR 0·54 (0·33 – 0·90); *0·018*	0·008
	Admission weight ≥1200 g	29/99 (29)	40/106 (38)	RR 1·29 (0·87 – 1·91); *0·206*	
	Singleton	41/90 (46)	30/94 (32)	RR 0·70 (0·48 – 1·02); *0·061*	0·008
	Twin pregnancy	14/45 (31)	21/40 (53)	RR 1·69 (1·0 – 2·86); *0·051*	
Exclusive breast feeding[a] at discharge, Nº (%)	Admission weight <1200 g	18/18 (100)	17/17 (100)	RR 1·0 (0·96 – 1·05); *0·.973*	NA
	Admission weight ≥1200 g	87/89 (98)	90/92 (98)	RR 1·0 (0·96 – 1·05); *0·973*	
	Singleton	71/71 (100)	75/76 (99)	RR 1·0 (0·93–1·13); *0·605*	NA
	Twin pregnancy	34/36 (94)	32/33 (97)	RR 1·0 (0·93 – 1·13); *0·605*	
Clinically suspected infection from 3 – 28 days, Nº (%)	Admission weight <1200 g	9/37 (24)	10/31 (32)	RR 1·33 (0·62 – 2·85); *0·470*	0·856
	Admission weight ≥1200 g	12/104 (12)	18/107 (17)	RR 1·46 (0·74 – 2·88); *0·277*	
	Singleton	16/96 (17)	22/97 (23)	RR 1·36 (0·76 – 2·43); *0·298*	0·959
	Twin pregnancy	5/45 (11)	6/41 (15)	RR 1·32 (0·43 – 4·0); *0·627*	
Blood culture confirmed infection from 3 – 28 days, Nº (%)	Admission weight <1200 g	0/37 (0)	1/31 (3)	RR 1·21 (0·33 – 4·41); *0·767*	NA
	Admission weight ≥1200 g	4/104 (4)	5/107 (5)	RR 1·21 (0·33 – 4·41); *0·767*	
	Singleton	2/96 (2)	3/97 (3)	RR 1·48 (0·25 – 8·71); *0·662*	0·935
	Twin pregnancy	2/45 (4)	3/41 (7)	RR 1·65 (0·29 – 9·39); *0·575*	
Duration of admission (h), mean	Admission weight <1200 g (n = 17; n = 17)	705·5	677·4	MD −28·1 (−174·5 – 118·4); *0·707*	0·595
	Admission weight ≥1200 g (n = 89; n = 91)	332·0	347·3	MD 15·2 (−48·4 – 78·9); *0·639*	
	Singleton (n = 70; n = 75)	410·8	404·1	MD −6·7 (−88·9 – 75·5); *0·873*	0·591
	Twin pregnancy (n = 36; n = 33)	355·2	388·2	MD 33·0 (−86·2 – 152·2); *0·588*	
Weight gain at 28+/−5d (g/day), mean	Admission weight <1200 g (n = 17; n = 16)	6·1	6·9	MD 0·8 (−6·64 – 8·19); *0·837*	0·369
	Admission weight ≥1200 g (n = 83; n = 88)	13·9	10·9	MD −2·9 (−6·19 – 0·33); *0·078*	
	Singleton (n = 65; n = 72)	12·9	11·2	MD −1·7 (−5·38 – 2·03); *0·377*	0·548
	Twin pregnancy (n = 35; n = 32)	11·9	8·2	MD −3·7 (−8·95 – 1·64); *0·177*	

Exclusively breastfeeding defined as only receiving breastmilk and no formula milk supplementation.
Abbreviations: CI = confidence intervals; h = hours; HR = Hazard ratio; IQR = Interquartile range; KMC = kangaroo mother care; MD = mean difference in intervention arm; NA = Not available; RR= risk ratio; SD = standard deviation.

Table 4
Provision of KMC to both trial arms, with measures of intervention adherence.

	Standard care (*N* = 141)	Early KMC (*N* = 138)
Received KMC at any time during admission, N° (%)	109 (77)	136 (99)
Age at starting KMC (h), median (IQR)	104·5 (73·4 – 166·1)	15·2 (10·7 – 22·0)
Started KMC within 24 h of admission, N° (%)	0 (0)	119 (86)
Time from admission to first KMC (h), median (IQR)	101·1 (71.·8 – 165·1)	12 (7·4 – 17·9)
First person to provide KMC, N° (%)		
Mother	98/109 (90)	73/136 (54)
Aunt	5/109 (5)	33/136 (24)
Grandmother	6/109 (6)	24/136 (18)
Other	0/109 (0)	6/136 (4)
Day 1: Duration in KMC position (h), median (IQR)	0 (0 – 0)	8.9 (5·4 – 11·7)
Day 2: Duration in KMC position (h), median (IQR)	0 (0 – 0)	7·4 (4·2 – 10·6)
Day 3: Duration in KMC position (h), median (IQR)	0 (0 – 0·1)	7·3 (2·6 – 10·5)
Day 4: Duration in KMC position (h), median (IQR)	0 (0 – 1·1)	6·8 (3·0 – 10·0)
Day 5: Duration in KMC position (h), median (IQR)	0 (0 – 3·0)	6·8 (1·8 – 9·5)
Day 6: Duration in KMC position (h), median (IQR)	0·7 (0 – 3·5)	5·8 (1·4 – 9·6)
Day 7: Duration in KMC position (h), median (IQR)	1·8 (0 – 6·0)	4·0 (0 – 9·2)
Total duration in KMC position (h), median (IQR)	21·6 (1·4 – 63·8)	66·8 (33·9 – 125·5)
Duration in KMC/day of enrolment (h), median (IQR)[a]	2·1 (0·2 – 3·7)	6·7 (4·3 – 8·5)
Days that ≥1 h of KMC provided, median (IQR)	5 (1 – 10)	9.5 (5 – 16)
Proportion discontinuing intervention, N° (%)	NA	46 (33·3)
Reason for discontinuation of intervention, N° (%)		
Severely unstable[b]	NA	16/46 (35)
Isolated apnoea needing resuscitation	NA	10/46 (22)
Severe jaundice	NA	8/46 (17)
Recurrent hypoglycaemia	NA	2/46 (4)
Severe abdominal distension	NA	2/46 (4)
Other[c]	NA	8/46 (17)
Age at stopping intervention (days), median (IQR)	NA	3·7 (1·6 – 6·2)
Proportion re-starting KMC once stability criteria met		22/46 (48)

a. 11% (15/138) of the intervention arm and 0.7% (1/141) of the control arm spent >10 h/d in KMC position from enrolment to discharge or last study visit if admitted beyond 28d of age.
a. Severe instability defined as per protocol criteria[18] and in Fig. 1.
b. Other reasons for discontinuation of the intervention were: seizures; omphalitis; neonatal skin infection; maternal skin infection; blood transfusion; non-severe presentation of infection; aspiration of milk; died (*n* = 1 each).
Abbreviations: CI = confidence intervals; *h* = hours; IQR = Interquartile range; KMC = kangaroo mother care; NA = Not available.

age 15·2 h). The longest time in the KMC position was on day one (median 8·9 h/day), reducing to between 4 – 7.4 h/day from day two (Table 4). Over three-quarters (77%, 109/141) of control participants received KMC during admission, none within the first 24 h and median 4·4 days old at initiation (Table 4, eFig.2).

There was no evidence of differences in the proportions of participants receiving concomitant oxygen (97% in control vs. 95% in intervention), bCPAP (13% vs. 14%), ampicillin and gentamicin (99% in both arms), gastric tube feeding (86% vs. 91%) and apnoea of prematurity prophylaxis (82% vs. 75%) during hospital stay. However, control participants received more meropenem (4 vs 0; p = 0·046) and less cefuroxime than intervention participants (0 vs 5; p = 0·023) (eTable 6).

4. Discussion

This randomised trial in a Gambian level 2+ neonatal unit did not provide evidence that early KMC for mild-moderately unstable neonates results in a mortality reduction compared with standard care. A halving of in-patient case-fatality rates (CFR) (48% pre-trial [15] vs. 23% during the trial) contributed to reduced power (~30%) to detect a 30% between-arm difference and the target sample size was not achieved. The median duration spent in KMC position for intervention participants was 6.7 h/day, reflecting known challenges in achieving prolonged KMC duration [24] and possibly contributing to the lack of effect. Secondary outcomes showed no between-arm differences, except for reduced hypothermia in neonates <1200 g.

The halving of baseline CFR in our cohort was likely influenced by both improvements to small and sick newborn care during the trial preparation phase (e.g. KMC implementation for stable newborns, increasing use of bCPAP) and enhanced clinical monitoring necessary for ethical trial conduct [25], protocol compliance and avoidance of performance bias.

Despite caregiver education and efforts to promote compliance, intervention neonates spent less than the recommended 18 h/day[6] in the kangaroo position, with median 6.7 h/day. The minimum threshold of KMC exposure for a mortality reduction to be achieved is not known [6,9] and mortality reductions are reported with >20 h/day [9] and >22 h/day [8]. The iKMC trial reported an increased risk of death for neonates receiving <10 h/day of skin-to-skin contact, but this may have been confounded by medical issues precluding longer durations [26]. Despite known benefits, ≥18 h/day KMC for stable neonates is often not achieved [24,27]. Promoting early KMC for unstable neonates for prolonged periods is even more challenging [28]. The longest duration spent in KMC position for our intervention neonates was during the first 24 h of trial participation (median 8.9 h/day), when neonates were still receiving oxygen, IV fluids and undergoing 6-hrly trial assessments. There-after, the daily duration reduced to between 4 h/day and 7.4 h/day. The iKMC trial achieved KMC duration of 16.9 h/day on the neonatal unit, with maternal support from dedicated study personnel [26]. Providing intensive health worker support for KMC was not possible within our trial as both research and hospital personnel had high workloads and multiple responsibilities with low nurse to patient ratios. KMC sessions were interrupted for medical procedures, routine neonatal cares (feeding, including expression of mother's milk) and for the KMC provider to rest, eat, pray and bathe. Other challenges to providing prolonged KMC duration included mothers being absent due to maternal illness, post-caesarean section or delivery at another health facility. This is reflected in nearly half of our intervention arm receiving first KMC

contact from a female relative (aunt/grandmother) and highlights the importance of family support for KMC [29]. The high proportion of twins (17% of our cohort were twins both enroled) may have also affected provision of prolonged KMC, due to the reticence of KMC providers to perform KMC with unstable twins simultaneously. The introduction of adult beds onto the NNU to enable continuous KMC was an important operational challenge, requiring re-organisation of patient flow, consideration of the infection prevention control implications and need to provide a respectful environment.

Our findings are in contrast to those from a small Ethiopian single centre trial reporting a 40% mortality reduction with KMC at < 24 h after delivery [30]. Detailed information on screening, randomisation and baseline stability were not reported, hence we cannot adequately compare populations and study design. However, a lower proportion received oxygen (~35% vs 89% in eKMC trial) and IV fluids (55% vs 86% in eKMC trial), suggesting a more stable cohort in the Ethiopian trial. The iKMC trial recently reported a 25% relative reduction in 28-day mortality (RR 0.75, 95% CI 0.64 −0.89, $p = 0.001$) with immediate KMC, started at 1.3 h after birth [27]. This multicentre trial recruited from five tertiary hospitals in India and Africa and identified statistically significant 28-day mortality reductions in the sub-groups of neonates 1.5 − 1.799 kg, singletons and those recruited at the Indian site [26]. An important difference with our trial was that iKMC sites had a higher level and quality of newborn care (WHO level 3), indicated by the lower control arm mortality rate of 15.7% and lower prevalence of hypothermia (10% vs 38−40% in our cohort) [26]. Information about the stability status of iKMC participants at baseline is not provided, hence we cannot make direct comparisons with our cohort. Another important difference was our inclusion of extremely low birth weight (<1 kg) neonates, comprising 11% of our cohort and not represented in the iKMC trial [26]. This may have further reduced intervention effects in our study due to the high risk of surfactant deficiency and our inability to simultaneously provide bCPAP and KMC.

In contrast to evidence that KMC improves stability scores at postnatal 6 h [8,13], we found no evidence of a difference at 24 h of enrolment. More detailed analyses are planned to compare with existing evidence that KMC positively regulates respiratory stability [8]. Our finding that KMC reduces hypothermia in neonates <1200 g is consistent with existing evidence [8,9] and has clinical significance for this population at greatest risk of hypothermia. Both arms were admitted for 16 days with no difference between arms. This is similar to the duration of stay of approximately two weeks reported by iKMC [26] and likely reflects the lack of effect of early KMC on weight gain and breastfeeding in our cohort, which were the main criteria for discharge.

The absence of effect of KMC on infections contrasts with previous meta-analyses reporting a 65% reduction in nosocomial infection [9] and 50% reduction in severe infection [8] with KMC in stable newborns. However, previous KMC trials used varied clinical infection definitions [8,9,26] and we are the first to report clear apriori clinical infection definitions combined with microbiologically confirmed infections and low-risk of detection bias. We found no evidence that KMC reduces infections, consistent with three previous studies reporting culture-confirmed infections which were included in the most recent Cochrane review [9]. The iKMC trial reported a 18% reduction in suspected sepsis with immediate KMC (RR 0.82, 95% CI 0.73 − 0.93) but used a non-validated non-specific clinical definition without microbiological confirmation. Two of the iKMC sites admitted control and intervention neonates to different NICUs, with newly built Mother-NICUs for the intervention arm [26]. Thus, the possibility of varying environmental exposures for nosocomial infections cannot be excluded and detection bias is also a risk. As for many LMIC neonatal units, infection prevention is a major challenge at EFSTH, with recent endemic *Burkholderia cepacia* and epidemic multi-drug resistant (MDR) *Klebsiella pneumoniae* outbreaks with contaminated intravenous fluids and antibiotics implicated in transmission [30,31]. This is consistent with the predominance of MDR-gram negative bacteria causing invasive infections in our cohort and, although we cannot comment on acquisition of invasive isolates, this warrants further study. It is possible that the effect of KMC on reducing infection risk may vary depending on the nosocomial context of the setting. Environmental exposures such as contaminated fluids and antibiotics are an infection risk regardless of when KMC is started and strengthening of infection prevention control procedures, including promotion of hand hygiene for KMC providers and health workers, should be ensured before KMC implementation and provision.

We cannot fully determine the safety of early KMC due to having low power for mortality, however we observed that it can be provided safely if continuous pulse-oximetry monitoring and targeted caregiver education are also in place. Pulse-oximetry monitoring should be part of safe oxygen provision for all neonates [6], yet is inconsistently available in many LMIC settings and was not widely available at the site prior to trial implementation. We advise caution to extrapolating our safety findings to settings without continuous pulse-oximetry monitoring, as one-third of the intervention group stopped KMC due to clinical deterioration and prompt detection of life-threatening conditions is essential. We recommend that neonates who are receiving KMC at the same time as oxygen should be continuously monitored with pulse oximetry.

eKMC is one of the first RCTs addressing the priority question of the mortality effect of early KMC in unstable neonates. Our results are generalisable to LMIC level 2/2+ neonatal units providing oxygen and continuous pulse-oximetry which have a high risk of nosocomial infection. As per Cochrane recommendations, we report clear definitions of eligibility and stability [9] and used a clinical infection definition based on a validated clinical score for preterm neonates [22] as well as reporting blood culture confirmed infections. We achieved high levels of protocol compliance for timing of KMC initiation, with a large between-group gap, but did not achieve targets of >18 h/day. KMC trials have some inherent limitations such as the inability to blind the intervention. Despite meticulous screening and allocation methods, there were minor differences in baseline stability between arms but these are probably due to chance and are not likely to have affected our results, as shown by the sensitivity analysis. We minimised performance bias by managing both arms in the same environment, implementing a standardised guideline and ensuring comparable between-group education. We had limitations in our data collection methods for KMC duration due to small size of our research team and possible under-estimation of KMC delivered due to high work-load and competing responsibilities. Accurate and validated methods of measuring KMC duration is a research gap with relevance for both routine health management information systems [24] and other KMC trials.

Due to improvements in survival and cessation of the trial before achieving the intended sample size, our trial had low power for the primary outcome but was adequately powered for some secondary outcomes. Our results may contribute to future meta-analyses and give safety and implementation insights into early KMC use in unstable neonates. Our methods and outcomes are purposefully similar to other, larger trials in LMIC [10].

More data about effectiveness and safety of early KMC is needed from settings with similar contexts of care. Understanding the minimum KMC duration needed for mortality effect is a key gap. Further research into infection prevention effects of KMC is needed with standardised definitions, microbiological and genomic analysis, including effects on neonatal microbiome and MDR-gram negative bacteria carriage. Implementation of KMC for any stability level is challenging and we urgently need more insights into how to promote prolonged KMC for stable and unstable neonates from health systems, health worker and mother/family perspectives, including economic evaluations.

The halving of mortality during the trial implementation period highlights the substantial survival gains possible with higher quality implementation of currently recommended small and sick newborn care. Due to low power, we cannot draw definitive conclusions about the mortality effects of early KMC in unstable neonates. However, our results may contribute to meta-analyses and provide important safety and implementation insights into the use of early KMC in unstable neonates on level 2/2+ special care neonatal units. Larger trials from similar settings are needed before policy and programmatic change can be recommended.

Contributors

HB and JEL conceived of the research question, obtained the funding and designed the trial with input from AR, CT and SC. The trial was implemented by HB, AG, BK, GW and ALS with data collection by AG, BK and GW. SD, MJ and BC were responsible for processing and reporting of microbiological data. SD was the laboratory analytical project manager. YN was responsible for data cleaning and verification. HB had access to the raw data and performed the statistical analysis with AKM. HB developed the figures and tables with exception of the supplementary heat map which was developed by AKM. HB wrote the original draft of the manuscript with critical revision for important intellectual content from JEL, AR, CT and SC. All authors contributed to the final version of the manuscript, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

We declare no competing interests.

Data sharing

Data sharing statement: De-identified individual participant data from eKMC trial database will be available in addition to data dictionary, study protocols, the statistical analysis plan and the informed consent form. The data will be made available after publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal, as agreed by the PI and assessed by MRCG Scientific Co-ordinating Committee. Proposals should be submitted to Dr Helen Brotherton [helen.brotherton@lshtm.ac.uk; hbrotherton@mrc.gm]. Data will be shared via secure methods and as per a signed material and data transfer agreement between MRCG at LSHTM and the requesting institution.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101050.

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OBJECTIVE 3

To explore pathways to mortality and physiological effects of early KMC prior to stability in neonates <2000g

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Chapter 7 - Pathways to mortality and physiological effects of early kangaroo mother care prior to stability in neonates <2000g

7.1. Scope of the chapter

This chapter will consider the pathways to mortality amongst neonates <2000g, with presentation of an original conceptual framework to understand mechanisms by which early KMC may affect key physiological factors in unstable neonates. In-order to understand the impact of changes to SSNC and eKMC trial participation during this PhD, in-patient mortality will be examined within three groups:1) All neonates before versus during the trial; 2) Neonates <2000g before versus during the trial; 3) Clinically eligible neonates who were recruited versus not-recruited to the trial. Pathways to mortality for unstable neonates <2000g will then be explored by 1) Identifying factors associated with mortality within the whole eKMC trial cohort and 2) Investigating between-arm differences for participants who died, including cause of death. The effect of KMC on any identified physiological risk factor will be investigated, focusing on the first 24h of KMC provision (referred to as the study period), as this is a clinically relevant period for improving physiological stabilisation for which we have detailed insights. Data from a variety of sources will be presented, with several related analyses, as summarised in Table 7-1.

Table 7-1. Overview of secondary analyses to understand changes to mortality, pathways to mortality and physiological effects of KMC prior to stability

Comparator groups		**Outcomes**	**Level & sources of data**	**Type of analyses**
Obj.1. Understand the changes to mortality before and during eKMC trial				
All admitted neonates Jan 2010 – Jan 2014	All admitted neonates Nov 2018 – Mar 2020	In-patient case fatality (CFR) rate, including birth-weight specific mortality	Population Published data[27] & prospective admission audit[a]	Observational (before-after)
All admitted neonates <2kg Jan 2010 – Jan 2014	All screened neonates <2kg May 2018 – Mar 2020			
Clinically eligible, recruited to eKMC (<2000g; <24h)	Clinically eligible, not recruited to eKMC (<2000g; <24h)	- Comparison of characteristics - In-patient CFR	Individual eKMC screening database[b]	Descriptive Generalised linear model
Obj.2. Understand pathways to mortality for unstable neonates <2000g				
eKMC participants who survived	eKMC participants who died	Predictors of 28-day mortality	Individual - eKMC database[c] - SAE forms[d]	Logistic regression
eKMC control group who died	eKMC intervention group who died	Clinical & physiological factors; Cause of death		Observational
Obj.3. Explore effects of early KMC on physiological factors				
eKMC control group	eKMC intervention group	Temperature; Glucose; Heart rate; SpO_2	Individual eKMC database[c]	Descriptive

a) Data available = outcomes (died, discharged) according to admission weight category; b) Data available = Weight, age, twin status, stability, heart rate, respiratory rate, SpO2, temp, glucose, examination, interventions received, outcome; c) Data available = All baseline characteristics, stability and physiological factors and outcomes; d) Data available = cause of death

7.2. Evidence for pathways to mortality and physiological effects of kangaroo mother care

7.2.1 Understanding pathways to mortality for neonates <2000g

Neonates weighing <2000g consist of neonates born preterm as well as those born growth restricted at term or before term gestation. The clinical syndromes, natural history, and prognosis for each of these groups is distinct, yet with some overlap. In settings without accurate prenatal and postnatal gestational age assessment tools it is not often possible to accurately distinguish between premature, LBW or SGA neonates on clinical grounds and birth weight <2000g is taken as a proxy for prematurity. For the purposes of this chapter, we will consider the pathways to mortality primarily for preterm neonates, although some of the pathways described are also relevant to growth restricted neonates, especially regarding feeding, nutrition, and infections.

The term "complications of prematurity" is based on ICD10 definitions[15] and covers a multitude of overlapping and interlinked pathophysiological processes which contribute to mortality. There is detailed data on causes and timing of preterm deaths from HIC[84] but a paucity of understanding of the pathways and exact causality of preterm death at population level in LMICs. Limited African and Asian pathology based surveillance data suggests multiple contributing factors, with infections playing a major role. [85] [86]

7.2.1.1 Complications of prematurity resulting in mortality

Complications of prematurity result from immature embryological and physiological development with major co-morbidities including: respiratory distress syndrome (RDS); intraventricular haemorrhage (IVH); apnoea of prematurity (AOP); necrotising enterocolitis (NEC). Infections due to an immature immune system can also be considered as a complication of being born preterm. Each of these important conditions will be considered in turn below with regards to their role in pathways to mortality for preterm neonates in resource limited settings.

7.2.1.1.1 Respiratory complications of prematurity

Respiratory distress syndrome (RDS) is due to the lack of production and release of surfactant, a lipopolysaccharide needed to maintain alveolar surface tension in the small airways of the lungs.[87] Surfactant is produced from 24 to 28 weeks of gestation, with sufficient quantities to enable adequate pulmonary-blood gas exchange present from ˜34 weeks. RDS occurs on a spectrum from mild respiratory distress which self resolves with minimal supportive care, to progressive respiratory distress, hypercapnia (high blood levels of carbon dioxide) and hypoxaemia (low blood oxygen levels) resulting in death within 3-4d after birth, if untreated.[88] RDS is the predominant cause of preterm mortality in LMIC settings and was responsible for an estimated 272,800 deaths in SSA in 2015[89] and 45% of deaths in an Ethiopian cohort of hospitalised preterm neonates as assessed by post-mortem methods.[86] The prognosis of RDS has been revolutionised in HIC during the past 50 years with antenatal steroids,[87] exogenous surfactant[90] and invasive respiratory support, with a recent shift towards less invasive surfactant administration and non-invasive respiratory support (e.g. CPAP) to prevent long-term sequelae associated with mechanical ventilation such as bronchopulmonary dysplasia (BPD).[91]

Apnoea of prematurity (AOP) occurs in neonates <34 weeks' gestation, with highest risk at <28 weeks. It is due to immaturity-related aberrant activity of central and peripheral chemoreceptors in the brainstem with insensitivity to hypercapnia and subsequent immature control of breathing. Poor

neuromuscular control of upper airway patency also contributes to the mixed central/obstructive apnoea.[92] The clinical syndrome encompasses a range of presentations from prolonged, unprovoked apnoea with associated bradycardia and desaturation, to brief pauses in breathing and periodic breathing with intermittent hypoxaemia. The contribution of AOP towards mortality of preterm neonates, including in LMICs, is not known. Prophylaxis with methylxanthines (caffeine citrate, aminophylline) is recommended until the preterm neonate matures and is better able to regulate their breathing.[93] Starting caffeine within 2d after birth also confers additional systemic benefits for the preterm neonate and is associated with reduced rates of BPD, patent ductus arteriosus and improved neurodevelopmental outcomes.[94]

7.2.1.1.2 Neurological complications of prematurity

Intraventricular haemorrhage (IVH) is a serious neurological disorder affecting preterm neonates with the most severe forms (grades 3-4) conferring a high risk of death, white matter injury or post-haemorrhagic hydrocephalus leading to neurodevelopmental disability. The global incidence rate of grade 3-4 IVH ranges from 6-22%, with high regional variation and lack of data from LMIC, especially African settings.[95] The aetiology involves immature blood vessel development around the germinal matrix in the lateral ventricles of the brain with subsequent high risk of haemorrhage. Advances in neuro-protective intensive care management, including minimal handling, avoidance of hypercapnia and rapid fluid shifts are important for prevention. Cranial ultrasound for early detection of IVH is a key component of SSNC and enables early intervention of subsequent post haemorrhagic hydrocephalus. Periventricular leukomalacia (PVL) is the commonest cause of white matter brain injury in preterm neonates, typically due to ischaemic or inflammatory injury to the developing brain. PVL is the commonest cause of motor disability and cerebral palsy in preterm survivors, with cranial USS and MRI preferred diagnostic methods and no current treatments. The prevalence and impact of PVL in preterm neonates born in resource limited settings is not yet known and the contribution to preterm mortality in low resource settings is not understood.

7.2.1.1.3 Gastro-intestinal complications of prematurity

NEC is an inflammatory disorder of the intestine linked to prematurity, formula milk feeds and antibiotic administration leading to intestinal dysbiosis, necrosis and systemic inflammatory response. [96]The timing of NEC onset is inversely proportional to gestational age, with more premature neonates developing it at a later postnatal age, typically >2 weeks after birth.[96] Prevalence peaks around 29 – 32 weeks' gestation with global incidence reported as 7%, although with large inter-regional variation and lack of African data.[97] Differentiation between NEC and infection is currently challenging and diagnosis relies on clinical and radiological criteria with management consisting of antibiotics, cessation of enteral feeds and surgical intervention in severe cases.

7.2.1.1.4 Infections as a complication of prematurity

Preterm neonates have deficiencies in both innate and adaptive immunity, such as impaired skin integrity, decreased neutrophil numbers and function and reduced immunoglobulin production.[98] The intestinal microbiome plays an important role in newborn immunity,[99] especially for preterm neonates who have altered microbiome composition and diversity compared to term neonates.[100] These differences are attributed to high antibiotic usage, prolonged exposure to hospital environment and immaturity[101] and include increased colonisation with facultative anaerobes

such as Enterobacteriaceae, reduced diversity and delay in development of protective commensal anaerobic bacteria.[102] The development, characterisation and role of alterations to the preterm intestinal microbiome in LMIC settings has not yet been described but is likely to be dominated by facultative anaerobes considering the high rates of Enterobacteriaceae intestinal colonisation reported from African and Asian settings.[103, 104] Preterm neonates in all settings are also particularly prone to invasive infections due to interventions such as plastic indwelling catheters and due to prolonged hospital stay, with neonatal units high risk for nosocomial infection.[105] Gram-negative bacilli, including the Enterobacteriaceae family (especially K pneumoniae and E coli) are the most common bacterial aetiology of sepsis in LMIC hospital born neonates[106] and African neonates[107] with multi-drug resistance in GNB invasive neonatal isolates an emerging public health priority.[108]

The CHAMPS multi-site African network (7 countries) reported that 62% (141/227) of neonatal deaths due to prematurity involved an infectious agent, based on post-mortem examinations and genomic diagnostics.[85] The SIP study also found that sepsis, pneumonia or meningitis was the primary aetiology in 30% of preterm deaths (331/1109) in Ethiopia.[86] A large cohort study at multiple tertiary centres in India identified a 12 – 16% population-attributable risk of mortality with culture-proven neonatal sepsis.[106] Early onset infections (<72h of age) due to vertical transmission linked to maternal carriage (e.g. Group B Streptococcus) or horizontal transmission linked to unhygienic birth practices[109] (e.g. Enterobacteriaceae or Staphylococcus aureus) may compound and mimic RDS. Late onset infections (>72h of age) may also have syndromic overlap with NEC, IVH and physiological jaundice.

7.2.1.1.5 Other co-morbidities associated with preterm mortality

Other co-morbidities which may be linked to the mortality pathway for neonates <2000g include milk aspiration due to underdeveloped oesophageal-gastric sphincter with uncoordinated suck/swallow and complications of jaundice, to which premature neonates are predisposed for physiological reasons. Premature birth may also be associated or triggered by co-morbidities such as early onset sepsis due to intrauterine acquisition of an infective agent, congenital infections, or genetic syndromes (e.g., trisomy 21). Similar to term neonates, intra-partum related asphyxia (IRA) may occur before or during delivery for preterm neonates resulting in neonatal encephalopathy (NE). The contribution of IPH or NE to mortality of premature neonates in LMICs is not fully understood, for multifactorial reasons including lack of fetal monitoring, absence of validated clinical scores validated in premature neonates[110, 111] and limited access to investigations to detect evidence of NE (cord and neonatal blood gases, neonatal brain imaging). Hence, only term neonates are included in global estimates of NE prevalence[112] and the contribution of IRA and NE towards the pathway to mortality in preterm neonates is not yet known.

7.2.1.2 Physiological factors contributing to pathways to mortality for neonates <2000g

Several physiological factors contribute towards adverse outcomes for neonates <2000g, with thermal and glycaemic control the most important, and cardio-respiratory instability the end result of many pathophysiological processes.

7.2.1.2.1 Thermal control

Temperature out-with the normal range (36.5°C to 37.5°C) is a well-recognised risk factor for mortality, with both hypothermia and hyperthermia at time of NNU admission associated with adverse outcomes in HIC[113] and LMIC settings.[114] Mortality risk increases with greater severity of hypothermia and in combination with other physiological disturbances such as hypoglycaemia and cardiorespiratory shock.[115] Preterm and growth restricted neonates are at high risk of hypothermia due to inefficient thermo-regulation from immature skin development, limited sub-cutaneous fat, lack of brown fat stores and inability to shiver for endogenous heat generation. Due to the relatively large surface-to-volume ratio and lack of cutaneous epidermis to retain heat, these neonates are also at risk of heat loss and inability to generate and maintain normothermia. The first 24h-48h after delivery represent the highest risk period for neonatal hypothermia.[115, 116] Hypothermia has a cascade effect with multi-system impact on metabolic and respiratory pathways and exacerbation of hypoglycaemia[115] and metabolic acidosis.[117] Hyperthermia refers to increased body temperature and may be environmental (e.g. high ambient temperature or iatrogenic due to inappropriately high incubator or radiant heater temperatures) or pathological in origin. Pathological causes of neonatal hyperthermia include inflammatory response to infection and central causes with dysregulation of normal thermal control due to hippocampal dysfunction. Hyperthermia shortly after delivery may also be due to maternal hyperthermia, which has been linked with adverse neonatal outcomes such as seizures and adverse neurological status.[118] Hyperthermia is associated with brain injury and haemodynamic changes[119] in addition to increased risk of neonatal mortality, [114] especially for neonates <1kg.[120]

7.2.1.2.2 Glycaemic regulation

Glucose is the major energy source for the neonate and tight glycaemic control is important for optimal physiology, with both hypoglycaemia[121] and hyperglycaemia[122] associated with increased neonatal mortality. Endogenous causes of hypoglycaemia in preterm neonates include a lack of glucose reserves due to limited glycogen and fat stores, impaired ability to generate glucose and higher metabolic demands. Exogenous reasons relevant to LMIC settings include reduced glucose provision from lack of access to IV dextrose[121] or parenteral nutrition and challenges in reliable monitoring of glucose levels. In addition to contributing to hypothermia[115] and mortality risk,[27] prolonged or recurrent hypoglycaemia during the early neonatal period is associated with long-term sequelae including impaired neuro-developmental and executive function as well as visuo-motor deficits.[123]

Hyperglycaemia is also a common complication of prematurity,[122] with an increased risk in neonates <1kg. It is associated with critical illness such as sepsis[124] but may also result from prematurity-related insulin resistance or deficiency,[125] activation of the hypothalamus-pituitary-adrenal (HPA) axis as part of the stress response with subsequent gluconeogenesis,[126] or due to iatrogenic excess glucose infusions.[127] The immediate effects of hyperglycaemia include osmotic diuresis and dehydration, increased risk of retinopathy of prematurity,[128] and worsening of respiratory distress syndrome and metabolic acidosis. Long-term sequelae of early hyperglycaemia include motor and language deficits.[129]

7.2.1.2.3 Autonomic nervous system, HPA axis & stress

The autonomic nervous system consists of the parasympathetic nervous system (PSNS; mediated primarily via the vagal and spinal nerves) and sympathetic nervous system (SNS; mediated via sympathetic nerve chain) which work in opposition to maintain cardio-respiratory stability (i.e., heart rate variability and blood pressure) and innervate visceral organs such as the gastro-intestinal tract. Neonates born at <28 weeks have impaired autonomic function with maturity developing up to 46 – 48 weeks postmenstrual age.[130] The hypothalamic-pituitary-adrenal (HPA) axis is an interactive neuro-endocrine unit which plays an important role in the body's response to stress via production of cortisol which activates the SNS.[131]

7.2.1.2.4 Cardiorespiratory instability, including hypoxaemia

Low blood oxygen levels (hypoxaemia) is common amongst unwell neonates and children in LMICs[132] and is linked to mortality, development of NEC and impaired neurodevelopment.[133] Conversely, hyperoxaemia (high blood oxygen levels) may harm premature neonates due to oxidative stress caused by generation of reactive oxygen species[134] and a relative deficiency in antioxidants contributing to BPD.[135] Retinopathy of prematurity and the resultant visual impairment results from abnormal retinal vascular growth due to fluctuations in blood oxygen levels with both hyperoxaemia and hypoxaemia as risk factors.[136] The peripheral blood oxygen saturation (SpO_2) is measured by non-invasive pulse oximetry and provides a proxy for the arterial oxygen concentration. Continuous SpO_2 measurement is standard of care in HIC and recommended for all neonates on oxygen in LMICs.[42] Several large RCTs (BOOST II, SUPPORT) have explored the optimal SpO_2 target ranges for preterm outcomes[133] yet the optimal SpO_2 range to promote survival and reduce the risk of ROP is not yet known.

The final common pathway to mortality for most complications of prematurity is cardiorespiratory instability, which may include hypercapnia, hypoxaemia, and fluctuations in blood pressure, perfusion and heart rate leading to the triad of apnoea, profound hypoxia, and bradycardia with subsequent cardio-respiratory arrest as the terminal event.

7.2.2 Mechanisms of effect for KMC in stable newborns

The mechanisms of KMC in stable neonates have been extensively explored in the literature and will be summarised below, considering the underlying primary mechanism, and linked to specific protective clinical effects. Most evidence for KMC mechanisms is derived from studies involving mothers, with a few studies comparing mechanisms between mothers and fathers[137-140] and none from aunties and grandmothers. Thus, evidence for mechanisms involving mothers as primary KMC provider will be considered below.

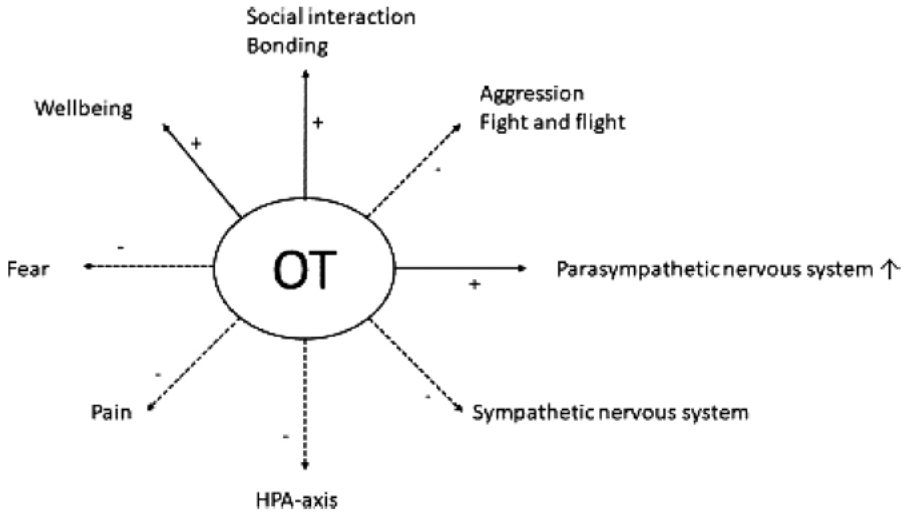
7.2.2.1 Neuroendocrine mechanisms underpinning beneficial effects of KMC

7.2.2.1.1 Oxytocin as key mediator of neuroendocrine pathways

During skin-to-skin contact in the KMC position, the neonate and the mother exchange a variety of visual, auditory, olfactory, and tactile stimuli, the so-called "sensory pathways", which activate the hypothalamus to release the neuropeptide oxytocin into the circulation and the brain.[141-143] Oxytocin enhances the PSNS, reduces the activity of the SNS and mediates activity in the HPA axis (Fig. 7-1).[143] This leads to multi-system physiological effects in both the neonate and the mother

which attenuates the pathophysiological processes related to preterm birth. As described below, the oxytocin-mediated physiological effects include: enhanced thermal control; cardio-respiratory stabilisation; reduction of pain, stress, and effect on glycaemic control; stabilisation of gastro-intestinal system; promotion of lactation and enhancement of maternal protective behaviours.

Figure 7-1. Oxytocin induced central effects associated with skin-to-skin contact



Source: Uvnas Moberg et al, 2020.[144] Reproduced with permission.

7.2.2.1.2 Effect of oxytocin on thermal control

Oxytocin release in the mother acts directly on blood vessels in the skin of her breasts, leading to vasodilation[145] and indirectly through reduction of the sympathetic nervous system,[141] thus increasing the skin temperature. The warmth and pulsatile pattern of slight variations in maternal skin temperature, combined with tactile stimuli from being next to the mother's chest, stimulates oxytocin release in the newborn. This results in generalised vasodilation in the neonatal skin with the greatest increase in the peripheries compared to the back or axilla due to greater sympathetic innervation of blood vessels in those areas.[146] Through this process, the maternal and neonatal skin temperatures equilibrate and rise in tandem[145] in a positive feedback loop. Encasing neonates in a dry wrapper or cloth with a hat additionally insulates them from heat loss due to convection, conduction, and radiation.

7.2.2.1.3 Effect of oxytocin on autonomic nervous system, HPA axis & intestinal hormones/microbiome

Oxytocin increases cardiac vagal tone via the PSNS resulting in increased heart rate variability, whereas the reduced sympathetic nervous tone results in decreases to heart rate and blood pressure. The decrease in HPA activity stimulated by oxytocin reduces cortisol production,[138] which then has downstream positive effects on glucose regulation and antioxidant production. The combination of reduced cortisol production, down-regulation of SNS and upregulation of PSNS has been attributed to reducing the "separation stress"' associated with removing neonates from their mothers.[130] Recently, the brain-gut-microbiota signalling system has been described as a mechanism by which oxytocin may contribute to stress reduction during KMC. This system includes bi-directional homeostatic communication from the brain to influence the motor, sensory, secretory and microbiome modalities of the gut and, conversely whereby the gut (including microbiome)

influences the HPA axis activity.[101] Neonatal oxytocin also directly stimulates release of gut hormones gastrin and cholecystokinin,[147] which aid digestion and promotes weight gain.

7.2.2.1.4 Effect of oxytocin on maternal breastmilk production, stress & behaviour

Maternal oxytocin release has a direct action on the anterior pituitary gland which releases prolactin and stimulates breast milk production in addition to circulating oxytocin acting on the breast ducts to release milk.[144] Maternal salivary cortisol levels and anxiety levels decrease during skin-to-skin contact with linked increase in salivary oxytocin.[142] The effect of oxytocin on mother's brains has also been linked to protective and caring behaviours of motherhood[145] and hypothesised to lead to increased vigilance and earlier detection of deterioration and severe illness.[144]

7.2.2.2 Breastmilk feeding promotion & support leading to beneficial effects of KMC

Promotion and support of breastmilk feeding is integral to the KMC package of care. The direct effects of oxytocin which enhance maternal milk supply[144] and neonatal gut stability[147] are complemented by an increased focus on feeding support as part of the care package and promotion by HCW. Breast milk confers multiple benefits to the premature neonate and is the preferred milk to improve outcomes by reducing risk of NEC[148, 149], late onset infections[150] and via promoting growth and development. The composition of human "preterm" breast milk is perfectly adapted to the needs of the preterm infant with high concentrations of protein and lipid compared to "term" breast milk and differences in digestive hormones, growth factors, vitamins, minerals and trace elements.[151] Breast milk contains a variety of bioactive immune factors, such as immunoglobulins,[99] inhibitory cytokines and factors involved in B cell differentiation and growth.[152] Breast milk also plays a central role in promoting a more stable and less diverse ("healthier") respiratory and intestinal neonatal microbiome.[99, 152]

7.2.2.3 Enhanced monitoring contributes to beneficial effects of KMC

KMC providers play an important role in cardio-respiratory monitoring during KMC[153] and may mitigate the impact of low staffing, limited access to monitoring devices and perceptions that KMC babies are low priority compared to more unwell neonates.[40] In addition to the effect of oxytocin on maternal behaviours (section 7.2.2.1.4), empowerment of KMC providers (mothers and families) through counselling and education increases knowledge of danger signs such as breathing difficulties[154] and may promote confidence in seeking timely help from HCW.

7.2.2.4 Mechanisms underpinning the infection prevention effects of KMC

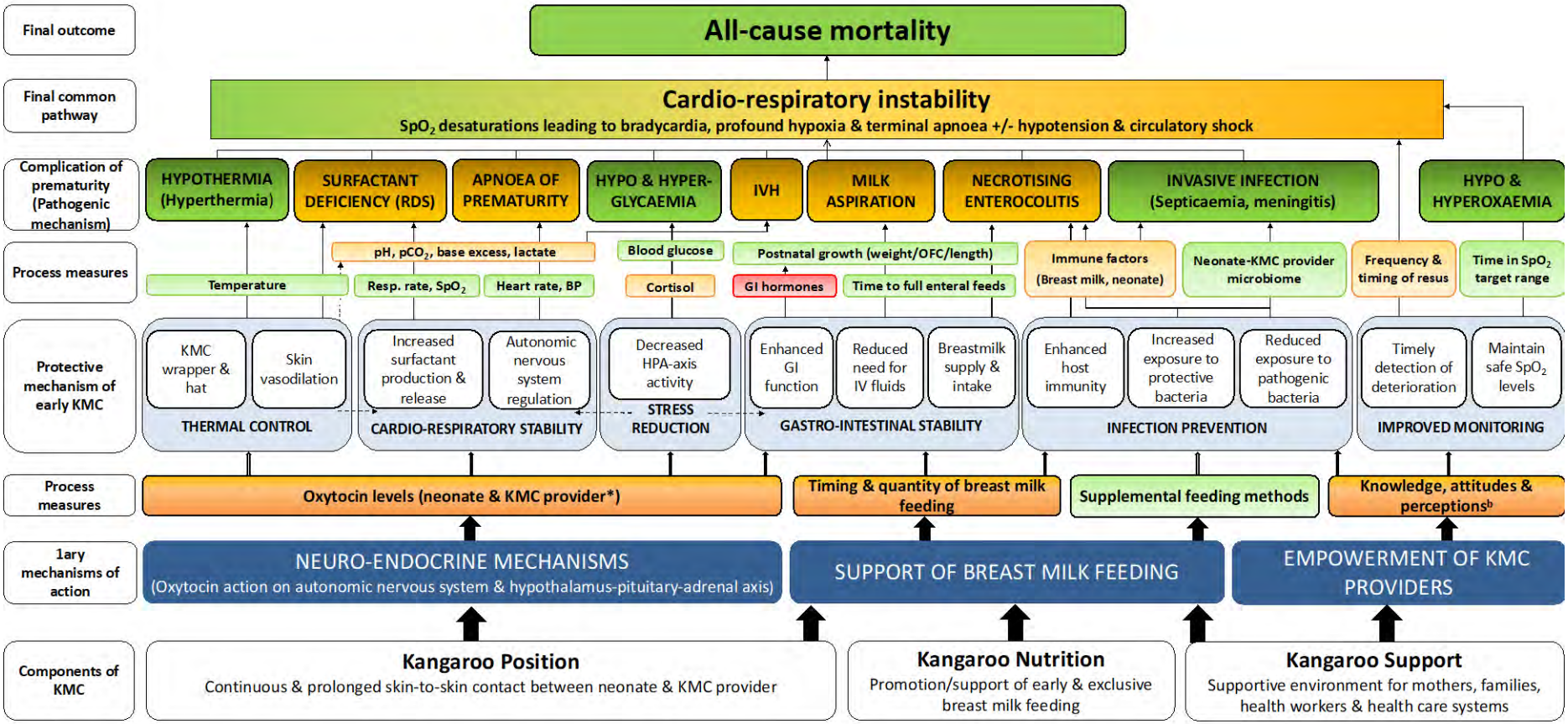
There is less robust mechanistic data for the infection prevention effects of KMC compared to other mechanisms. Potential mechanisms which have been hypothesised include: (1) Reduced exposure to pathogenic bacteria from being in the KMC position and "shielding" from the environment; (2) Enhanced exposure to maternal commensal bacteria[155] (3) Beneficial changes to neonatal gut microbiome via the brain-gut-microbiome signalling system;[101] and (4) immunity related benefits from enhanced breastmilk intake (section 7.2.2.2). Modulation of the neonatal microbiome is highly likely to be involved in underlying mechanisms and there is some evidence from HIC settings that KMC alters the oral microbiome with reduced Pseudomonas spp. and increased Streptococci spp. after intermittent KMC.[155] Intermittent KMC (2h/day for 7d) was also associated with an increased risk of nasal decolonisation of staphylococcus aureus, including MRSA.[156] Taken together, these studies suggest that KMC may change the landscape of neonatal bacterial carriage, but the precise

mechanisms of KMC effect on infections, including immunity pathways, microbiome and AMR acquisition, have not yet been fully elucidated, especially in high infection burden settings.

7.2.3 Conceptual framework to understand how KMC prior to stability may affect pathways to mortality

A conceptual framework was developed as part of this PhD to understand potential mechanisms by which early KMC may influence the pathways to mortality for unstable neonates <2000g, especially during the initial 24h of KMC provision. The framework was based on known pathophysiological factors involved in the pathways to neonatal mortality (section 7.2.1) and existing evidence for KMC mechanisms in stable neonates (section 7.2.2) with extrapolation to an unstable population (Fig. 7-2). This framework will enable a structured approach for considering the pathways to mortality for mild-moderately unstable neonates <2000g and the effect of early KMC on physiological factors, which is the focus of the mechanistic analyses described in the following sections of this chapter.

Figure 7-2. Conceptual framework to understand how early kangaroo mother care prior to stability may influence pathways to mortality for neonates <2000g



Green = measurable during eKMC trial; Orange = Not measurable during eKMC trial but may be possible to measure in future research; Red = Not measurable.
Abbreviations: BP = Blood pressure; GI = Gastro-intestinal; HPA = Hypothalamic-pituitary-adrenal; IVH = Intraventricular haemorrhage; KMC = Kangaroo mother care; OFC = Occipital-frontal circumference; pCO_2 = partial pressure of carbon dioxide; RDS = Respiratory Distress Syndrome; SpO2 = Oxygen saturation.

7.3. Objectives and methods for mechanistic analyses

7.3.1 Objectives of exploratory mechanistic analyses

The three objectives for these exploratory analyses are:

1. To understand changes to mortality during the eKMC trial
2. To identify risk factors for mortality within the eKMC trial population of mild-moderately unstable neonates <2000g and understand if there were clinical or sociodemographic differences in neonates who died in each allocation arm
3. To explore the effect of early KMC on selected physiological factors which are associated with mortality

7.3.2 Data collection

7.3.2.1 Mechanistic analysis Obj.1. Understand the changes to mortality during the eKMC trial

Retrospective inpatient case fatality data for all neonates and neonates <2000g for the period 2010 – 2014 were obtained from a published mortality audit conducted at EFSTH with additional data on admission-weight specific in-patient case fatality rates supplied by the author.[27]
Prospective inpatient case fatality data was collected during the trial recruitment period (23rd May 2018 to 19th March 2020) by research nurses using a trial register to document all admissions and outcomes. Considering the unreliability of birth weight measurements outside of the trial setting and the high rates of admissions from a range of health facilities, we took the admission weight as proxy for birthweight. All admitted neonates were weighed by the EFSTH team on the ward digital scale (5g gradation), with this weight documented in the trial register for neonates weighing >2000g. If the EFSTH scale weight was ≤2000g, neonates were re-weighed by the eKMC team using the study scale (Seca 750, 2g gradation) with this weight documented in the register. Readmissions were not distinguished but occurred in 0.9% of all screened neonates (10/1107) and are not likely to have affected the results. Outcome data (discharged or died) were recorded in the register for each admitted neonate using medical records, nursing logs and death certificates as source documents.

All neonates <2000g who were assessed for eKMC eligibility criteria had the following data recorded on the electronic screening RedCAP database: sex; admission weight; age at admission (hours); singleton or twin/triplet status; referral site; and date/time of admission. Singleton or twin neonates aged <24h who were not already recruited to another MRCG study then underwent a clinical screening process involving physical examination and assessment of cardiorespiratory stability over ten minutes using a Nonin 2000A pulse oximeter (heart rate and SpO_2) and manual measurement of respiratory rate, presence of severe chest indrawing and apnoea requiring bag-valve-mask ventilation. The stability assessment could be performed a maximum of three times during the screening process: 1) initial screening 2) repeat screening after 3 hours if moderate or severely unstable 3) re-check of stability prior to recruitment if caregiver available >3h since last screening. Only data from the first screening period was included in this analysis. All clinical and stability data from these screening events were documented on the electronic RedCAP screening database, as well as medications and usual care interventions (e.g., oxygen) provided before and during screening.

Screened participants were divided into three categories for the purpose of this analysis:

1. Ineligible for eKMC trial: Neonates not meeting inclusion criteria (i.e., Age >24h or weight ≥2000g) or with ≥1 of the following exclusion criteria: mother or newborn recruited to another MRCG study; triplet with all admitted; congenital malformation incompatible with life or needing immediate surgery; seizures; severely unstable; died during screening
2. Clinically eligible, not recruited: Mild-moderately unstable neonates who were not recruited due to either unavailable study bed, no willing caregiver within 24h of admission, or no consent provided
3. Clinically eligible, recruited: Recruited to eKMC trial

Pre-discharge outcome data (died/discharged) for all screened neonates were reconciled from the trial register into the screening database post-hoc.

7.3.2.2 Mechanistic analysis Obj.2. Understanding pathways to mortality for unstable neonates <2000g

Baseline characteristics, physiological and outcome data for recruited neonates were extracted from the eKMC participant database, with data collected as outlined in chapter 5. Cause of death for eKMC participants was taken as stated on the final serious adverse event (SAE) report form, which was determined prospectively by the PI on review of the medical records and following discussion with health workers involved with the patient. If cause of death was not obvious, the medical records were reviewed with the eKMC local safety monitor (LSM), a West African Consultant Paediatrician, with consensus between the PI and LSM reached about the most likely cause of death. Cause of death data were not collected for non-recruited neonates, in recognition that cause of death attribution at EFSTH was done by the most junior medical personnel without investigations or post-mortems and was likely to be unreliable.

7.3.2.3 Mechanistic analysis Obj.3. Explore effect of early kangaroo mother care on physiological factors for unstable neonates <2000g

All neonates recruited to the eKMC trial were included in this exploratory analysis, with the intention of maintaining the original randomisation sequence. Although temperature and stability were reported as secondary outcomes during the eKMC trial, they were defined and measured at a single time point, 24h of enrolment, which didn't take into consideration changes over the preceding 24h and within-subject dependence. Similarly, stability was measured as a composite score (aSCRIP) of cardiorespiratory parameters at 24h after enrolment with no consideration of individual components of stability or how stability changed over time. Hypoglycaemia was not a secondary outcome in the eKMC trial but, considering the importance of glycaemic control in the pathway to mortality and high proportion of neonates receiving IV fluids alongside early KMC, it was identified as a priority variable for this mechanistic analysis.

Axillary temperature, blood glucose and cardiorespiratory parameters were measured at baseline, and 6-hourly for the initial 24h after enrolment, as per eKMC trial protocol.[10] Temperature was recorded using a low-reading digital thermometer, with 3 consecutive measurements and a mean value automatically calculated in the electronic CRF. Blood glucose was measured as a point of care test using a calibrated glucometer. Six-hourly spot checks of respiratory rate (manually observed), heart rate and SpO_2 (observed from Nonin 2000A pulse oximeter readings) were documented every

minute for 10 minutes in the electronic CRF with mean values automatically calculated. Categorical variables were generated for each continuous parameter (e.g., temperature, blood glucose) in STATA according to protocol definitions of normal physiological ranges.

7.3.3 Statistical considerations

All statistical analyses were performed using STATAv16 (Stata Corp., College Station, TX, USA). The clinical significance of mortality reductions and risk factors were assessed by considering the point estimates generated with measures of the uncertainty using 95% confidence intervals.[157] As missing data was low (<5%) and assumed to be missing completely at random, complete case analysis was used for missing outcome data.

7.3.3.1. Statistical methods to understand mortality changes at study site during PhD

Inpatient case-fatality rates (CFR) for all admitted neonates and those <2000g (of all ages) were calculated with neonates admitted during the trial period as the denominator and those with confirmed deaths as the numerator. This was compared with the pre-trial crude inpatient CFR rates as a before-after comparison.

Baseline clinical and socio-demographic factors in clinically eligible neonates who were recruited versus not recruited were compared to identify differences which could have affected mortality risk. Wilcoxon-Mann-Whitney test was used to generate p values for continuous variables and Chi squared test for categorical variables. Comparison of in-patient outcomes (died or discharged) between recruited versus non-recruited groups was done using a generalised linear model (binomial variance, log link), adjusting for potential confounding factors identified as being significant in the descriptive analysis. Reliable gestational age data were not available for the non-recruited group; hence this variable was not included in the model.

The temporal trends in admissions and mortalities were visually explored using bar-line graphs, by calendar month for the duration of the eKMC recruitment period (May 2018 to March 2020). This was done to explore trends in seasonality of admissions and mortality for (1) All neonates <2000g who were screened and (2) Clinically eligible neonates recruited and not-recruited. Seasonality was defined as per previously described rainy/dry seasonal patterns in The Gambia with the rainy season occurring from 1st July to 30th November.[71] Previous studies have shown higher preterm and SGA birth rates during the rainy season[71] and it was hypothesised that this may result in higher mortality due to higher hospital admission rates and overcrowding with reduced access to life saving interventions such as bCPAP.

7.3.3.2 Statistical methods to understand pathways to mortality for unstable neonates <2000g

Clinical and physiological factors were selected based on the conceptual framework for pathways to mortality (Fig. 7-2). Continuously distributed variables were re-categorised into categorical form using threshold values consistent with normal neonatal physiologic ranges and eKMC trial protocol definitions.[10] Physiological variables measured at baseline and during the first 24h of study period were re-categorised at 3-factor levels (abnormal at baseline; became abnormal during first 24h; not abnormal at any timepoint) and considered as one categorical variable to reduce risk of collinearity. Univariate logistic regression was used to assess for associations between each predictor variable and 28-day mortality. Variables from the univariate analysis with evidence of an association with

death (P<0.05) were included in a multivariate binomial logistic regression model, with odds ratios (OR) and 95% confidence intervals calculated for each variable. Considering that gestational age was not assessed with the gold standard tool (first trimester ultrasound) and that New Ballard score is an unreliable predictor of gestational age,[158] only admission weight was used in the multivariate regression model. As this was a post-hoc analysis, no sample size calculation was performed. The causes and distribution of timing of deaths for all eKMC participants were presented.

7.3.3.3 Statistical methods to explore the effect of KMC prior to stability on physiological factors

The crude median/mean values (dependent on distribution) and proportion of neonates with a clinically relevant abnormality were calculated for each treatment arm at each 6-hourly time-points, e.g., proportion hypothermic at 6h, 12h, etc., and presented as profile plots with 95% confidence intervals to assess for any pattern of between-arm differences. Between-arm differences at each discrete time-point were explored, using chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous variables. Within-subject correlation was anticipated due to the nature of the dependent variables, short period between observations, and time needed for abnormal values to normalise. Hence, if the descriptive analysis identified evidence of between-arm differences in categorical variables at individual time-points with no over-lapping of the 95% confidence intervals, further exploration was planned with generalised estimating equations (GEE), for categorical dependent variables and random-effects models for continuous dependent variables, including adjustment for the baseline value of the dependent variable being studied and admission weight.

7.4. Results

7.4.1 Understanding mortality changes before and during the eKMC trial

7.4.1.1 Overview of inpatient case fatality rates before and during the eKMC trial

Inpatient CFR reduced for all admitted neonates from 35.1% (1,734/4,944) to 27.6% (486/1,759) (21% relative reduction) from the pre-trial period (2010 – 2014) versus the eKMC trial (2018 – 2020) respectively (Table 7-2). There was a 24% relative reduction in the CFR for all neonates <2000g from 47.7% (770/1,615)18 to 36.1% (383/1061) during the same period. The CFR of mild-moderately unstable neonates <2000g who met clinical eligibility criteria for the trial and were recruited was 22.6% (63/279) versus 29.1% (78/268) for clinically comparable neonates who were not recruited. (Table 7-2). This is considered further in section 7.4.1.4 following an additional analysis adjusting for baseline differences between the two groups.

Table 7-2. Changes to inpatient case-fatality rates at EFSTH neonatal unit during the eKMC trial

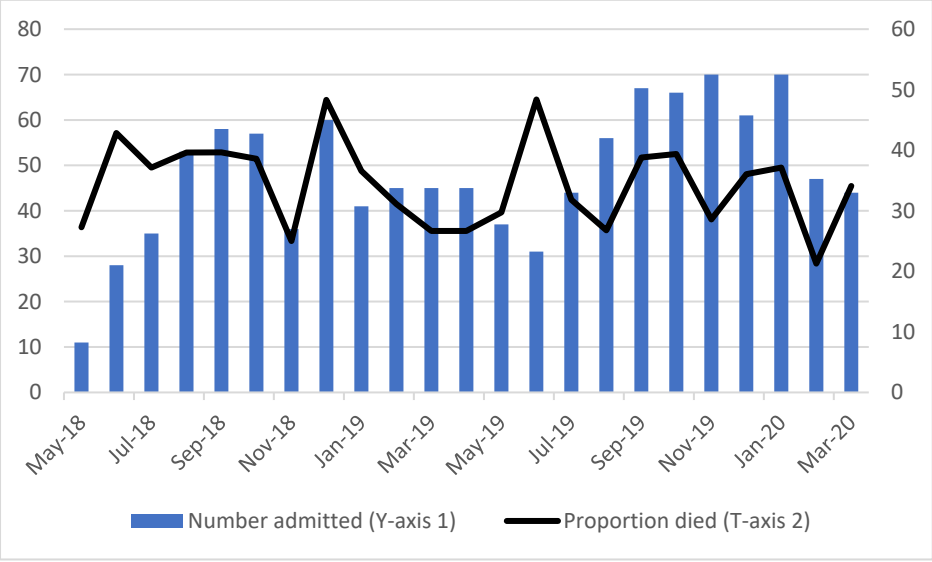
Time period	Population	Case fatality rate Inpatient deaths/ admissions (%)
All neonates admitted to EFSTH NNU		
Jan 2010 – Jan 2014	All admitted	1734 / 4944 (35.1%)[a]
Nov 2018 –March 2020		486 / 1759 (27.6%)
Neonates ≤2000g admitted to EFSTH NNU		
Jan 2010 – Jan 2014	Admission weight <2000g	770 / 1615 (47.7%)
May 2018 –March 2020	All screened (<2000g, all ages)	383 / 1061[b] (36.1%)
	Ineligible for eKMC trial[c]	242 / 514 (47.1%)
	Clinically eligible, not recruited[d]	78 / 268 (29.1%)
	Clinically eligible, recruited[d]	63 / 279 (22.6%)

a) Published audit data from EFSTH NNU;[27] b) 1107 neonates were screened with outcome data available for 1061; c) Included: neonates aged >24h at admission; weight ≥2 kg on study scales; severely unstable; stable; congenital malformation or seizures; d) Restricted to neonates aged <24h at admission, weight <2kg and mild-moderately unstable.

7.4.1.2 Temporal trends in admission and mortality for all screened neonates <2000g

During the trial period, a seasonal admission pattern was observed for all screened neonates <2000g, with peaks during the rainy season (August-November) and lowest rates during the dry season (January-July)(Fig.7-3). However, the proportion of screened neonates who died did not show a clear seasonal pattern or obvious temporal relationship with periods of more intense NNU admission. As screening and recruitment began towards the end of May 2018 the numbers of neonates admitted in May 2018 is artificially low. Also, the proportion of screened neonates <2000g who died did not appear to reduce during the course of the eKMC trial (Fig.7-3).

Figure 7-3. Temporal trends in admissions and inpatient mortality for all screened neonates <2000g during eKMC trial

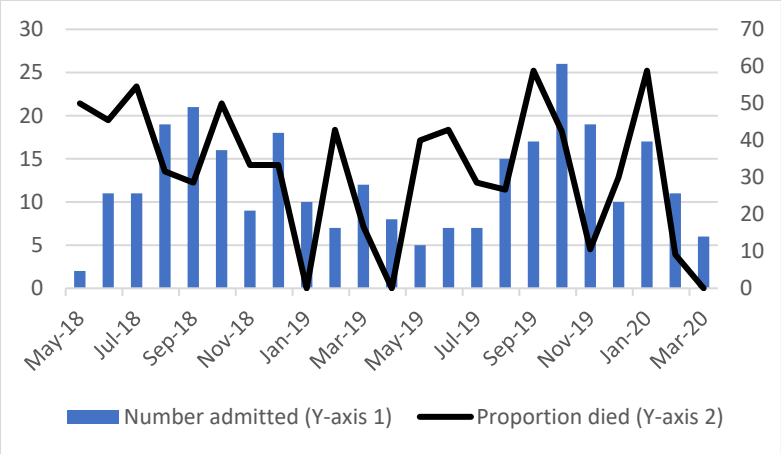


7.4.1.3 Mortality trends for mild-moderately unstable neonates <2000g

7.4.1.3.1 Seasonal mortality trends for mild-moderately unstable neonates <2000g

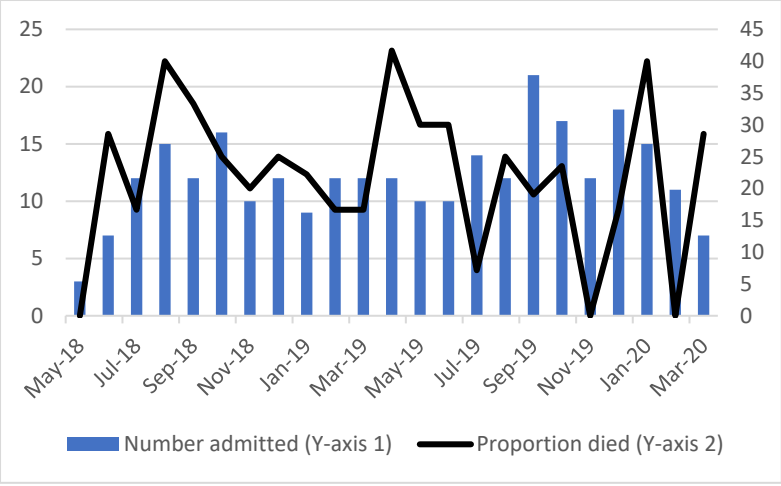
Mild-moderately unstable neonates who were not recruited had a similar seasonal pattern of admissions as that observed in the larger cohort of all screened neonates <2000g (Fig.7-4).

Figure 7-4. Mild-moderately unstable neonates not recruited to eKMC trial: admissions & proportion of mortalities by calendar month (n=268)



However, eKMC participants were admitted more consistently over the trial period with less of a seasonal mortality pattern observed on visualisation of the data (Fig.7-5). Proportion of deaths, relative to admissions, did not appear to follow a seasonal trend for either the recruited or non-recruited groups of mild-moderately unstable neonates (Fig.7-4, Fig.7-5). Recruited neonates died consistently through-out the trial period with no apparent trend of mortality reducing over time (Fig.7-5).

Figure 7-5. Recruited mild-moderately unstable neonates: admissions & proportion of mortalities by calendar month (n=279)



7.4.1.3.2 Characteristics of mild-moderately unstable neonates <2000g

Clinically eligible neonates who were not recruited were admitted at a younger age (median 1.17h vs. 2.3h, p=0.003) and were more likely to be referred from the EFSTH maternity unit (assumed inborn)(61% vs. 44%, p<0.0001) compared to clinically comparable neonates who were recruited to

the eKMC trial. The proportion of twins in the recruited group (31%) was also higher than the non-recruited group (23%). Other features were similar between the groups, with no evidence of important differences in weight and sex (Table 7-3).

Table 7-3. Comparison of socio-demographic, clinical features, and outcomes for mild-moderately unstable neonates <2000g recruited versus not recruited to the eKMC trial

	Recruited N= 279	**Not recruited[a] N= 284**	**Effect size (95% CI)**	**p value**
Male sex, N° (%)	118/278 (42)	126 (44)	-	0.542
Weight (g), median (IQR)	1450 (1180 – 1656)	1500 (1200 – 1741)	-	0.120
Weight distribution, N° (%)				0.609
<1200g	73 (26)	68 (24)	-	
≥1200g	206(75)	216 (76)	-	
Twin, N° (%)	86 (31)	66 (23)	-	0.059
Age at admission (h), median (IQR)	2.3[b] (0.78 – 5.25)	1.17[c] (0.65 – 3.33)	-	0.003
Night shift admission,[d] N° (%)	119[e] (43)	124[e] (45)	-	0.669
Rainy season admission,[f] N° (%)	136 (49)	150 (53)	-	0.334
Referred from EFSTH,[g] N° (%)	123 (44)	173 (61)	-	<0.0001
Axillary temperature (°C), median (IQR)	36.1[h] (35.5 – 36.8)	36.2[i] (35.5 – 36.9)	-	0.189
Blood glucose (mmol/L), median (IQR)	3.7[j] (3 – 4.7)	3.7[k] (2.8 – 5.2)	-	0.934
Respiratory rate (bpm), median (IQR)	58[l] (49 – 70)	58[m] (48 – 68)	-	0.995
Heart rate (bpm), median (IQR)	139[l] (128 – 153)	141[m] (131 – 155)	-	0.140
SpO_2 (%), median (IQR)	98[n] (95 – 99)	97[m] (95 – 98)	-	0.274
SpO_2 <88%, N° (%)	16/271 (6)	15/253 (6)	-	0.990
NMR-2000 score, median (IQR)	17.6[o] (14.8 – 19.6)	18.3[p] (15.0 – 20.2)	-	0.083
Inpatient mortality,[q] N° (%)	63 (22.6)	78[b] (29.1)	RR: 0.71 (0.53 – 0.96)	0.026

a) Met clinical criteria but not recruited due to lack of study bed, absence of caregiver within 24h of admission or consent declined; b) n = 268; c) n = 263; d) Night shift defined as 20:00 – 07:59; e) n = 278; f) Rainy season from June to October; g) Data on place of birth not collected during screening, but place of referral assumed to be place of birth due to age <24h at admission; h) n = 266; i) n = 261; j) n = 259; k) n= 255; l) n = 207; m) n = 191; n) n= 206; o) n = 210; p) n = 195; q) Adjusted for twin status, admission age and place of referral
Abbreviations: bCPAP = bubble CPAP; bpm = beats per minute; CI = confidence intervals; cpm = cycles per minute; EFSTH= Edward Francis Small Teaching Hospital; IQR=Interquartile range; NMR-2000 = Neonatal Mortality Score-200071; RR = Risk ratio

7.4.1.3.3 Inpatient case fatality rates for recruited vs. not recruited mild-moderately unstable neonates <2000g

Neonates recruited to the eKMC trial had a 29% reduced risk of dying during NNU admission compared to mild-moderately unstable neonates who were not recruited to the eKMC trial (22.6% vs. 29.1%, RR = 0.71, 95% CI 0.53 – 0.96, p=0.026)(Table 7-3). This included adjustment for age at admission, twin status, and place of referral (assumed to be place of birth), as important between-group differences (section 7.4.1.3.2).

7.4.2 Mortality risk factors for mild-moderately unstable neonates <2000g (eKMC participants)

7.4.2.1 Clinical & physiological factors associated with 28-day mortality

23% (63/279) of all mild-moderately unstable neonates recruited to the eKMC trial died: 24% (34/141) in the control arm and 21% (29/138) in the intervention arm (Table 6-2). Univariate analysis identified 11 variables associated with mortality within the eKMC trial cohort (Table 7-4), including: gestational age <32 weeks; admission weight <1200g; hypothermia; hyperglycaemia; abnormal heart rate; hypoxaemia <88% and resuscitation given at delivery. Multivariate analysis identified 6 variables associated with an increased odds of dying within 28-days. The variables showing strongest evidence of association were: admission weight (OR=3.76, 95% CI 1.89 – 7.49, p <0.001); resuscitation at delivery (OR=3.98, 95% CI 1.04 – 15.1, p=0.043); hypothermia at baseline (OR=2.53, 95% CI 1.25 – 5.11, p=0.01); hyperglycaemia during first 24h of trial enrolment (OR=2.46, 95% CI 1.24 – 4.88, p=0.01); and hypoxaemia at baseline (OR=5.49, 95% CI 1.08 – 27.97, P=0.040) (Table 7-4). Of note, neither hypoglycaemia at baseline nor during the initial 24h study period was associated with increased odds of mortality.

Table 7-4. Clinical and physiological factors associated with 28-day mortality in the eKMC trial cohort

Clinical feature				**Univariate analysis**	**Multivariate analysis**
	Total N (%) N=277	**Survived[a] N (%) N=214**	**Died[a] N (%) N=63**	**Odds ratio (95% CI) p value**	**Odds ratio (95% CI) p value (n=265)**
Clinical & temporal factors					
Male sex	116 (42)	90 (43)	26 (41)	0.97 (0.55 – 1.71) p=0.911	-
Admission weight <1.2kg	72 (26)	39 (18)	33 (52)	4.94 (2.71 – 9.00) p <0.0001	OR=3.73 (1.87 – 7.47) p <0.001
Gestational age <32 weeks	84 (30)	46 (22)	38 (60)	6.82 (3.64 – 12.77) P <0.0001	-
Twin pregnancy	86 (31)	69 (32)	17 (27)	0.78 (0.42 – 1.45) p=0.428	-
Resuscitation at delivery[b]	15/276 (5)	7 (3)	8/62 (13)	4.38 (1.58 – 12.17) p=0.003	OR=3.66 (1.01 – 13.2) P=0.048
Perinatal septic risk factors[c]	86 (31)	66 (31)	20 (32)	1.04 (0.57 – 1.90) p=0.892	-
Born at EFSTH (inborn)	119 (43)	97 (45)	22 (35)	0.65 (0.36 – 1.16) p=0.143	-
Born during rainy season	138 (50)	107 (50)	31 (49)	0.97 (0.55 – 1.70) 0.912	-
Physiological factors					
Hypothermia at baseline	120/275 (44)	81/212 (38)	39 (62)	2.63 (1.48 – 4.67) p <0.001	OR=2.53 (1.25 – 5.11) p=0.01
Hypothermia from 6-24h[d]	226 (82)	169 (79)	57 (90)	2.53 (1.05 – 6.08) p=0.038	OR=1.71 (0.58– 5.06) p=0.334
Hyperthermia at baseline	27/275 (10)	19/212 (9)	8 (13)	1.48 (0.63 – 3.49) p=0.382	-
Hyperthermia from 6-24h[d]	93 (34)	71 (33)	22 (35)	1.08 (0.60 – 1.94) p=0.797	-

Hypoglycaemia at baseline	13/273 (5)	10/210 (5)	3 (5)	1.0 (0.29 – 3.50) p=1.000	-
Hypoglycaemia from 6-24h[d]	58 (21)	47 (22)	11 (17)	0.75 (0.37 – 1.54) p=0.440	-
Hyperglycaemia at baseline	32/273 (12)	19/210 (9)	13 (21)	2.61 (1.22 – 5.59) p=0.012	OR=1.68 (0.65 – 4.31) p=0.284
Hyperglycaemia from 6-24h[d]	91 (33)	59 (28)	32 (51)	2.71 (1.53 – 4.82) p <0.001	OR=2.46 (1.24 – 4.88) p=0.01
RR <20 or >60 at baseline	111/272 (41)	79/209 (38)	32 (51)	1.70 (0.97 – 2.97) p=0.066	-
RR <20 or >60 from 6-24h[d]	185 (67)	145 (68)	40 (63)	0.83 (0.46 – 1.48) p=0.528	-
HR <100 or >200 at baseline	4/271 (1)	1/208 (0.5)	3 (5)	10.35 (1.45 – 0.84) p=0.014	OR=3.63 (0.20 – 65.6) p=0.383
HR <100 or >200 from 6-24h[d]	12 (4)	5 (2)	7 (11)	5.23 (1.68 – 16.2) p=0.003	OR=4.90 (1.07 – 22.5) p=0.041
Hypoxaemia at baseline	9/270 (3)	3/210 (1)	6/60 (10)	7.67 (2.03 – 28.86) p=0.001	OR=5.81 (1.13 – 29.78) p=0.035
Hypoxaemia from 6-24h[d]	18 (6)	8 (4)	10 (17)	4.86 (1.88 – 12.56) p <0.001	OR=2.51 (0.70 – 9.01) p=0.158
Hyperoxaemia at baseline	192/270 (71)	152/210 (72)	40/60 (67)	0.28 (0.02 – 4.50) p=0.366	-
Hyperoxaemia during 24h[d]	273 (99)	212 (99)	61 (97)	0.33 (0.02 – 5.59) p=0.445	-

a) Unless stated otherwise, N=214 for those who survived and N=63 for those who died; b) Resuscitation at birth with one or more of: oxygen, bag-valve-mask ventilation, or chest compressions; c) Perinatal septic risk factors defined as one or more of: prolonged rupture of membranes >18h; maternal fever within 48h of delivery; offensive smelling liquor or chorioamnionitis; d) One or more episodes during the 24h period under study

7.4.2.2 Cause and timing of death

Infection was the most assigned cause of death in both arms, accounting for over half of all deaths (56%, 19/34, in control arm; 55%, 16/29, in intervention arm). Suspected or confirmed late onset infections were responsible for similar proportions of deaths in both arms, with 45% (13/29) in intervention arm and 41% (14/34) in control arm (Table 7-5). The 7 neonates who died due to confirmed late onset infection all had gram-negative bacilli isolated from blood culture, of which 88% (7/8) of isolates were phenotypically multi-drug resistant (MDR) (Chapter 6, eTable-4).

Suspected RDS with or without suspected infection, was the assigned cause of death for 14% (4/29) of deaths among those receiving KMC compared to 34% (12/34) of deaths among the standard care group. Cause of death was attributed to hypoglycaemia in 4 neonates (2 per treatment group) due to unrecordable blood glucose level at time of resuscitation and no other clinically apparent reason for death. Two neonates in the intervention arm died due to aspiration pneumonitis following a discrete episode of milk aspiration, in addition to two neonates who died due to aminophylline or IV fluid administration errors (one of each) (Table 7-5). Post-mortem examinations were not conducted for any deaths, due to cultural and religious expectations that neonates would be buried as soon as possible and lack of a professional culture of conducting neonatal post-mortem examinations. All deaths occurred during hospitalisation, although deaths in the community beyond 28 postnatal days were not ascertained, as this was beyond the trial follow-up period. Time from enrolment to death

was explored as part of the secondary trial outcome analysis and showed no difference in median time to death between groups using cox regression (Chapter 6).

Table 7-5. Causes and timing of death in eKMC trial population, by treatment group

	Standard care	Early KMC
	N=34	N=29
Cause of death, No (%)		
Infection (all) Suspected early onset sepsis Suspected late onset sepsis[a] Confirmed late onset sepsis[b]	19 (56) 5 (15) 10 (29) 4 (12)	16 (55) 3 (10) 10 (34) 3 (10)
Suspected respiratory distress syndrome (RDS)	12 (34)	4 (14)
Apnoea of prematurity	1 (3)	1 (3)
Complications of milk aspiration	0	2 (7)
Hypoglycaemia	0	2 (7)
Other[c]	1 (3)	2 (7)
Unknown[d]	1 (3)	2 (7)
Age at death, No (%)		
<24h	5 (15)	2 (7)
25 – 72h	11 (32)	7 (24)
73h – 7d	13 (38)	12 (41)
7 – 28d	5 (15)	8 (28)

a) Met protocol criteria for suspected late onset sepsis and blood culture was negative for known pathogen; b) Met protocol criteria for suspected late onset sepsis and blood culture was positive for known pathogen; c) Other causes of death were a suspected inherited muscular disorder (control), an aminophylline overdose leading to acute cardio-respiratory arrest (intervention) and suspected fluid overload resulting from over-administration of IV fluids; d) Post-mortems were not conducted but scrutiny of case records by PI and LSM did not reveal a clinically obvious cause of death

7.4.3 Effect of early kangaroo mother care prior to stability on physiological factors

Physiological factors identified as being risk factors for mortality on multivariate analysis (section 7.4.2.1, Table 7-4) were investigated further to explore whether early KMC was associated with any differences. Abnormal respiratory rate (<20 or >60 bpm) occurred in two-thirds of the cohort during the study period but was not associated with mortality, hence was not explored further.

7.4.3.1 Participant characteristics and intervention/control adherence

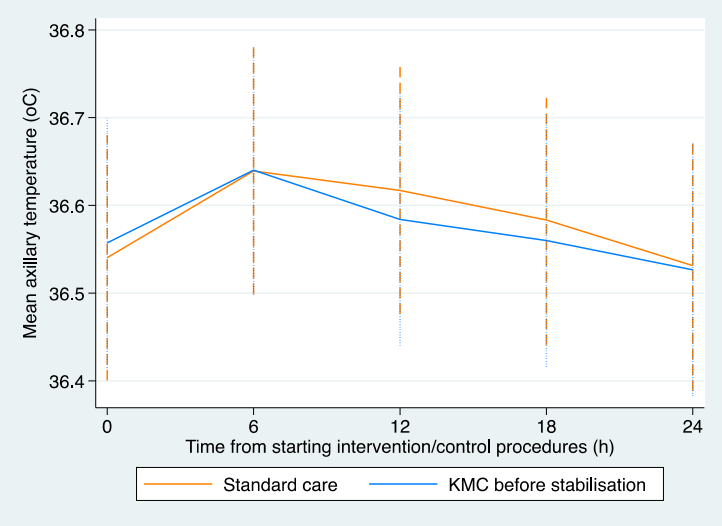
Baseline characteristics were comparable between allocation arms except for a greater proportion of intervention neonates stable at baseline and more control neonates received AOP prophylaxis prior to allocation (Table 6-1, eTable6-1). Supplemental oxygen or bCPAP was provided to 97% (269/277) of the cohort during the period of study, with the majority (94%, 259/277) receiving only low-flow oxygen from concentrators via nasal cannula. During the period under study (first 24h of enrolment), 97% (134/138) of the intervention arm and none in the control arm received care in the kangaroo position, with median duration 8.9h (range 0 - 19.2h) in the intervention arm (Table 6-4).

7.4.3.2 Effect of early kangaroo mother care on physiological factors

7.4.3.2.1 Thermal control

1,086 temperature observations were analysed from 279 neonates (141 in control arm; 138 in intervention arm). Missing data were minimal (2.8%) and equal across both arms. The mean temperature remained constant at 36.5–36.6 °C throughout the period in both groups (Fig. 7-6).

Figure 7-6. Mean axillary temperature at 6 hourly intervals, during first 24h of eKMC trial enrolment



Hypothermia occurred at least once during the first 24h of enrolment in 82% (226/277) of mild-moderately unstable neonates <2000g (Table 7-4), with 6-hourly point prevalence ranging from 34 – 45% (control) and 36 – 45% (intervention) (Table 7-6, Fig.7-7). Of the neonates who were hypothermic at baseline, only 17% (10/59) in the control arm and 15% (10/66) in the intervention arm achieved and maintained their temperature within the normal range for the following 24h period. For neonates with temperature within the normal range at baseline, 82% (67/82) of the control arm and 75% (54/72) in the intervention arm subsequently developed hypothermia over the following 24h.

Figure 7-7. Hypothermia prevalence at 6-hourly intervals, during first 24h of eKMC trial enrolment

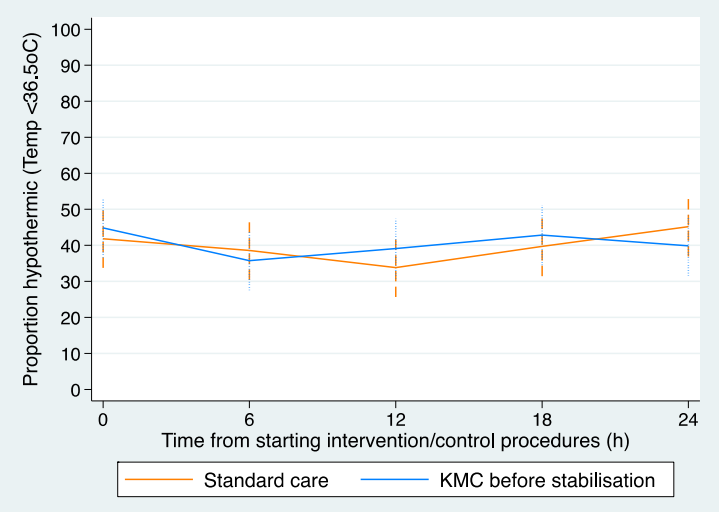
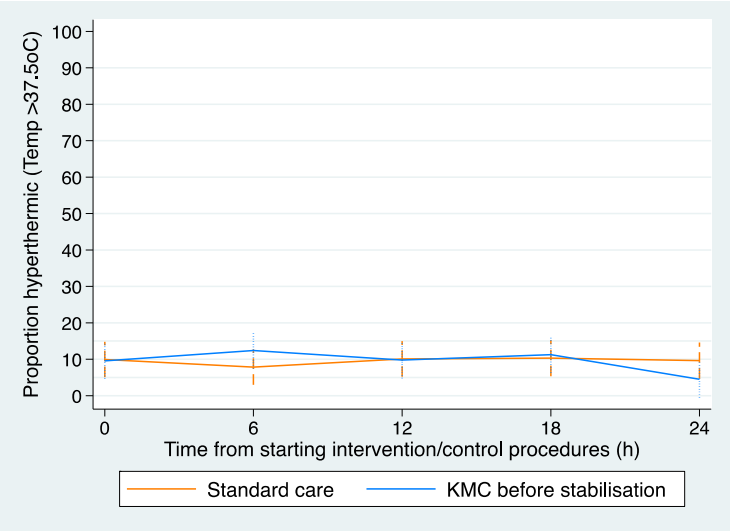


Table 7-6. Thermal control during first 24h of enrolment, by treatment group

	Standard care	Early KMC	p value
Baseline (T0)	**N=141**	**N=136**	
Axillary temperature, °C mean, (SD)	36.5 (0.88)	36.6 (0.87)	0.836
Hypothermia (T<36.5°C), N° (%)	59 (42)	61 (45)	0.613
Hyperthermia (T>37.5 °C), N° (%)	14 (10)	13 (10)	0.917
6 hours	**N=140**	**N=137**	
Axillary temperature, °C mean, (SD)	36.6 (0.74)	36.6 (0.86)	0.864
Hypothermia (T<36.5 °C), N° (%)	54 (39)	49 (36)	0.629
Hyperthermia (T>37.5 °C), N° (%)	12 (9)	18 (13)	0.209
12 hours	**N=139**	**N=133**	
Axillary temperature, °C mean, (SD)	36.6 (0.76)	36.6 (0.93)	0.540
Hypothermia (T<36.5 °C), N° (%)	47(34)	52 (39)	0.365
Hyperthermia (T>37.5 °C), N° (%)	14 (10)	13 (10)	0.935
18 hours	**N=136**	**N=133**	
Axillary temperature, °C mean, (SD)	36.6 (0.77)	36.6 (0.88)	0.784
Hypothermia (T<36.5 °C), N° (%)	54 (40)	57 (43)	0.600
Hyperthermia (T>37.5 °C), N° (%)	14 (10)	15 (11)	0.795
24 hours	**N=135**	**N=133**	
Axillary temperature, °C mean, (SD)	36.5 (1.0)	36.5 (0.69)	0.665
Hypothermia (T<36.5 °C), N° (%)	61 (45)	53 (40)	0.377
Hyperthermia (T>37.5 °C), N° (%)	13 (10)	6 (5)	0.103

Hyperthermia occurred less frequently than hypothermia, with 10% of neonates hyperthermic in both arms at baseline and during the 24h period (Fig. 7-8). There was no indication of between-group differences in mean temperature (Fig. 7-6), proportion hypothermic (Fig.7-7) or hyperthermic (Fig.7-8) at each 6-hourly time point for the first 24h of enrolment (Table 7-6).

Figure 7-8. Hyperthermia prevalence at 6-hourly intervals, during first 24h of eKMC trial enrolment



7.4.3.2.2 Glycaemic control

1,075 observations from 279 neonates (141 in control; 138 in intervention) were analysed. Mean blood glucose was within normal physiological range for both groups at each 6-hourly time point (Fig. 7-9, Table 7-7) with no evidence of between-arm differences detected (Table 7-7).

Figure 7-9. Mean blood glucose levels at 6-hourly intervals, during first 24h of eKMC trial enrolment

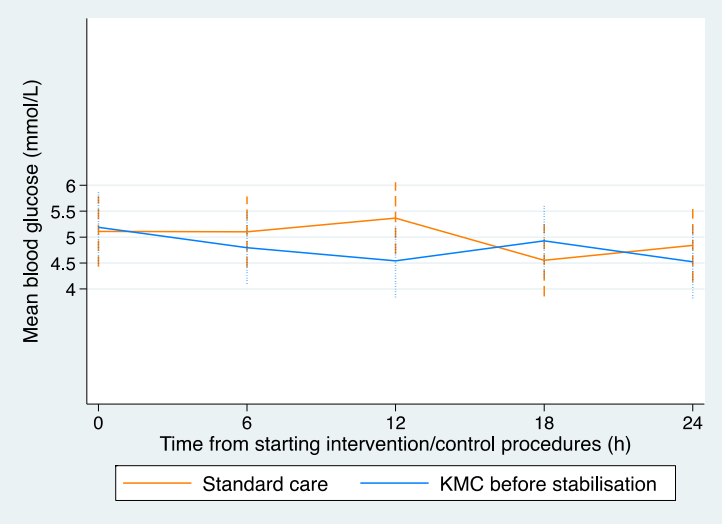
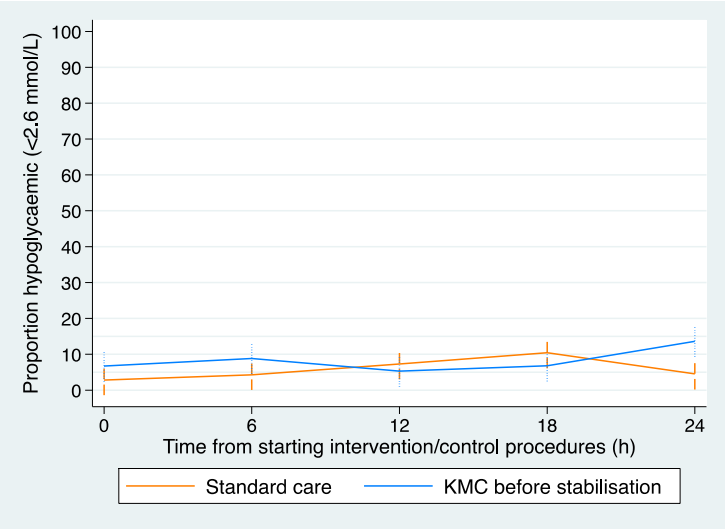


Table 7-7. Glycaemic control during first 24h of enrolment, by treatment arm

	Standard care	**Early KMC**	**P value**
Baseline (T0)	**N=141**	**N=134**	
Blood glucose (mmol/L), mean, (SD)	5.11 (3.3)	5.19 (5.0)	0.132
Hypoglycaemia,[a] Nº (%)	4 (3)	9 (7)	0.130
Hyperglycaemia,[b] Nº (%)	19 (13)	13 (10)	0.329
6h	**N=141**	**N=138**	
Blood glucose (mmol/L), mean, (SD)	5.1 (4.1)	4.80 (3.8)	0.185
Hypoglycaemia,[a] Nº (%)	6 (4)	12 (9)	0.127
Hyperglycaemia,[b] Nº (%)	17 (12)	16 (12)	0.923
12h	**N=137**	**N=132**	
Blood glucose (mmol/L), mean, (SD)	5.37 (4.9)	4.54 (3.2)	0.193
Hypoglycaemia,[a] Nº (%)	10 (7)	7 (5)	0.501
Hyperglycaemia,[b] Nº (%)	19 (14)	13 (10)	0.309
18h	**N=134**	**N=132**	
Blood glucose (mmol/L), mean, (SD)	4.55 (3.5)	4.93 (4.8)	0.848
Hypoglycaemia,[a] Nº (%)	14 (10)	9 (7)	0.292
Hyperglycaemia,[b] Nº (%)	11 (8)	12 (9)	0.798
24h	**N=132**	**N=132**	
Blood glucose (mmol/L), mean, (SD)	4.84 (3.7)	4.52 (4.5)	0.057
Hypoglycaemia,[a] Nº (%)	6 (5)	18 (14)	**0.010**
Hyperglycaemia,[b] Nº (%)	16 (12)	9 (7)	0.141

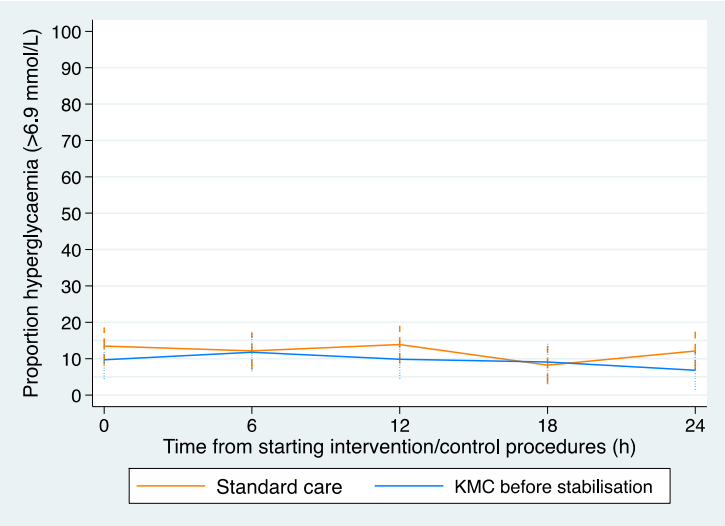
Neonates in the intervention arm were more likely to be hypoglycaemic at 24h (18/134 (14%) compared to the control arm (6/141 (5%), P=0.01) (Fig. 7-10, Table 7-7). A significant effect was not observed on repeated measure analysis adjusting for covariates (RR 0.98. 95% CI 0.95 – 1.01. p 0.215) and this difference was possibly observed by chance, due to multiplicity of testing.

Figure 7-10. Hypoglycaemia prevalence at 6-hourly intervals, during first 24h of eKMC trial enrolment



Hyperglycaemic events were observed in 7%-12% of neonates in the intervention arm compared to 8%-14% of neonates receiving standard care (Fig. 7-11), with no evidence of between-arm differences at 6-hourly time points (Table 7-7).

Figure 7-11. Hyperglycaemia prevalence at 6-hourly intervals, during first 24h of eKMC trial enrolment



7.4.3.2.3 Cardiorespiratory stability

7.4.3.2.3.1 Heart rate

1084 heart rate observations were analysed, with 3% missing data, equal between allocation groups. Mean heart rate was within normal range for both treatment groups (134.0 – 141.8 in control arm; 136.6 – 138.0 in intervention arm) (Fig. 7-12, Table 7-8). The proportion of neonates with an abnormal heart rate (<100 bpm or >200 bpm) at any time during the observation period ranged from 0 – 2% in the control group and 0.8% – 3.0% in the intervention group, with overlapping confidence intervals and no evidence of between-arm differences observed (Table 7-8).

Figure 7-12. Mean heart rate at 6-hourly intervals, during first 24h of eKMC trial enrolment

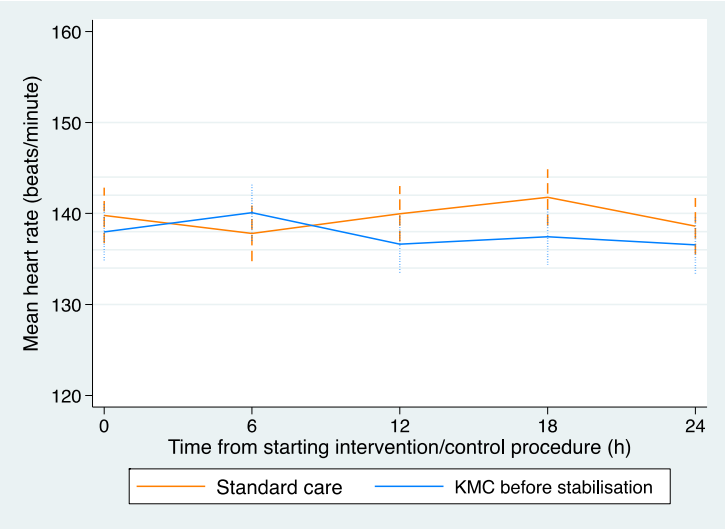


Table 7-8. Heart rate and oxygen saturation at 6-hourly intervals, during first 24h of enrolment

	Standard care	**Early KMC**	**p value**
Heart rate			
Baseline (T0)	**N=139**	**N=134**	
Heart rate, (bm) mean, (SD)	139.8 (17.3)	138.0 (18.0)	0.246
Abnormal heart rate[a] N° (%)	3 (2)	1 (0.8)	0.332
6h	**N=138**	**N=137**	
Heart rate, (bm) mean, (SD)	137.8 (18.6)	140.1 (17.7)	0.271
Abnormal heart rate[a] N° (%)	2 (1)	2 (1)	0.988
12h	**N=139**	**N=134**	
Heart rate, (bm) mean, (SD)	134.0 (18.3)	136.6 (17.1)	0.310
Abnormal heart rate[a] N° (%)	0	4 (3)	0.040
18h	**N=136**	**N=134**	
Heart rate, (bm) mean, (SD)	141.8 (20.3)	137.4 (19.8)	0.124
Abnormal heart rate[a] N° (%)	1 (0.7)	2 (1)	0.553
24h	**N=135**	**N=131**	
Heart rate, (bm) mean, (SD)	138.6 (20.0)	136.6 (15.7)	0.182
Abnormal heart rate[a] N° (%)	3 (2)	1 (0.8)	0.328
Oxygen saturation			
Baseline (T0)	**N=140**	**N=132**	
SpO2 (%), median (range)	96.8 (74 – 100)	97.1 (81 – 100)	0.921
Hypoxaemia (<88%), N° (%)	5 (4)	4 (3)	0.803
Hyperoxaemia (>95%), N° (%)	100 (71)	94 (71)	0.969
6h	**N=137**	**N=136**	
SpO2 (%), median (range)	97.3 (68 – 100)	97.3 (41.3 – 100)	0.742
Hypoxaemia (<88%), N° (%)	3 (2)	3 (2)	0.993
Hyperoxaemia (>95%), N° (%)	102 (75)	101 (74)	0.862
12h	**N=139**	**N=134**	
SpO_2 (%), median (range)	97 (82.3 – 100)	97.4 (64 - 100)	0.612
Hypoxaemia (<88%), N° (%)	3 (2)	2 (1)	0.682
Hyperoxaemia (>95%), N° (%)	102 (74)	102 (76)	0.603
18h	**N=137**	**N=134**	
SpO_2 (%), median (range)	97 (68 – 100)	97 (82 – 100)	0.500

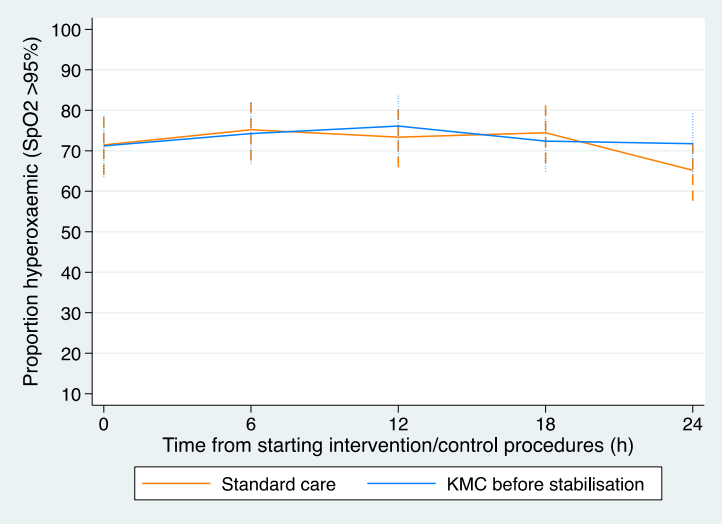
Hypoxaemia (<88%), N° (%)	1 (0.7)	1 (0.8)	0.987
Hyperoxaemia (>95%), N° (%)	102 (75)	97 (72)	0.700
24h	**N=135**	**N=131**	
SpO_2 (%), median (range)	96.2 (79 – 100)	97 (78.7 – 99.6)	0.234
Hypoxaemia (<88%), N° (%)	3 (2)	2 (2)	0.676
Hyperoxaemia (>95%), N° (%)	88 (65)	94 (72)	0.249

a) Abnormal heart rate defined as <100 or >200 bpm

7.4.3.2.3.2 Peripheral oxygen saturation

Median SpO_2 was between 95% - 97% during the first 24h of enrolment in both groups. Prevalence of hypoxaemia was low (0.7 – 4.0% in both arms) but hyperoxaemia occurred in 71% (192/270) of all eKMC participants at baseline and 99% (273/277) of neonates at one or more time point within the first 24h of enrolment (Table 7-4). The point prevalence of hyperoxaemia at each 6-hourly time point was 65% – 75% with no evidence of between-arm difference for hypoxaemia or hyperoxaemia (Fig. 7-13, Table 7-8).

Figure 7-13. Hyperoxaemia prevalence at 6-hourly intervals, during first 24h of eKMC trial enrolment



7.5. Discussion of the findings of the mechanistic analyses

We identified substantial mortality reductions compared to the pre-trial period for all neonates admitted to the trial site (21% relative reduction) and all small and sick neonates (<2000g) (24% relative reduction). Clinical trial participation was associated with 29% reduced risk of mortality compared to non-recruited, clinically comparable neonates. Despite these survival gains, inpatient case fatality rates at the study site were still high at 28% (all neonates) and 36% (all <2000g) during the trial period. We identified particularly high rates of hypothermia and hyperoxaemia during the first 24h after eKMC trial enrolment, corresponding to the first 48h after birth for our cohort. Weight <1200g, early hypothermia and hypoxaemia were associated with increased odds of mortality. Deaths occurred predominantly within the first 7d after birth due to infections, especially late-onset infections, with gram-negative bacilli responsible for all confirmed infections and high MDR prevalence. We did not identify any beneficial or deleterious effects of early KMC on thermal control, glycaemic control, or cardiorespiratory stability. These key findings will be discussed below in relation to the literature, with consideration of the strengths and limitations of these exploratory analyses.

7.5.1 Reduced neonatal mortality compared to pre-trial period

There are multiple possible reasons why the all-cause neonatal mortality rates may have reduced during the eKMC trial period compared to the pre-trial period. Maternal and perinatal interventions such as appropriate antenatal corticosteroids for threatened preterm labour, antibiotics for prolonged rupture of membranes and skilled birth care and resuscitation all have high potential to impact on neonatal mortality.[39, 89] Exploration of such changes at EFSTH maternity unit is limited due to lack of local data from the pre-trial period and high rates of missing data on antenatal steroid and antibiotic use within our cohort. There were substantial improvements to provision and quality of SSNC, including KMC, between 2014 and 2018, to which this PhD contributed (Chapter 3). Provision of bCPAP was a major difference. Modelling estimates have identified a nearly 50% reduced risk of perinatal mortality with bCPAP use for management of RDS (RR 0.52, 95% CI 0.32 – 0.87).[89] Likewise, introduction of KMC with associated training and enhanced focus on IPC may have also contributed to improved survival. The substantial mortality effect of clinical trial enrolment may also reflect closer clinical scrutiny and monitoring inherent to clinical trials, highlighting the direct benefits of conducting clinical research in resource limited settings as well as the importance of monitoring in the pathway to mortality for preterm neonates. These findings will be discussed in more detail in Chapter 8.

7.5.2 Neonatal mortality still unacceptably high

Despite the impressive mortality reductions, the observed mortality (28% CFR) for all neonates during the trial period was higher than elsewhere in the sub-region and underlines the need for continuing attention to SSNC and high quality monitoring if SDG 3.2 target is to be met by 2030. Other published inpatient mortality rates in West-Central Africa range from 16% in Cameroon,[159] 9 - 20% in Ghana[160-162] and 14% in Nigeria.[163] However, comparing inpatient mortality rates is complicated by different spectrums of illness severity, heterogeneous gestational age and weight profiles and varying contexts of newborn referral systems and care within and between countries. The higher rates we observed may be influenced by EFSTH being the referral NNU and linked to the tertiary maternity unit, thus admitting more severely unwell neonates following complicated pregnancies or deliveries. This discrepancy in mortality by health facility level has also been reported in Ghana, where the level 2+ NNUs in tertiary centres have higher inpatient CFR (19.2%)[162] compared to regional and district hospitals (8.9%; 8.5%).[160] The weight-specific mortality rate of 36% within our cohort of neonates <2000g is also slightly higher than inpatient mortality rates reported from other West African NNUs with similar provision of non-intensive care. For example, Tette et al reported 32% CFR (33/158) for neonates <2000g admitted to a newly established regional hospital in a deprived rural region in Ghana.[160]

7.5.3 Risk factors for neonatal mortality

7.5.3.1 Lower gestational age and weight are integral to pathways to mortality for neonates <2000g

Decreasing gestational age and birth weight are known to be strong predictors of neonatal mortality and gestational age particularly plays a key role in the pathway to mortality through increasing the risk of complications of prematurity, especially RDS, NEC, IVH and late onset infections.
Gestational age <32 weeks was associated with nearly 7-fold increased risk of dying in the eKMC trial cohort (RR 6.82, 95% CI 3.62 – 12.83, p<0.0001). This is similar to epidemiological estimates[34] and post-mortem based studies,[86] showing an inverse relationship between gestational age and

mortality with greatest risk in neonates <28 weeks. We identified that neonates with admission weight <1200g had a nearly 5-fold higher odds of dying within 28d, compared to neonates >=1200g (OR=4.94, 95% CI 2.70 – 9.03. P<0.0001). Neonates <1kg are at particular risk with neonates <500g having a universal risk of mortality in resource limited non-intensive care settings.[162]

7.5.3.2 Importance of thermal control in pathways to mortality

The eKMC trial population had a very high prevalence of hypothermia (axillary temperature <36.5^{o}C) during the first 24h of enrolment with 82% (226/277) of neonates hypothermic at least once and 34 – 45% point prevalence.

Neonatal hypothermia is a recognised global problem with high impact on neonatal outcomes, and wide variations in prevalence at health facility and community levels. The prevalence of hypothermia from hospital-based studies in 4 African countries ranges from 44% - 69% in Zambia to 62% – 68% in Nigeria with the highest prevalence of 85% at time of admission to a tertiary hospital in Zimbabwe.[115] Weight-specific prevalence rates in LMICs are even higher, with reported 38% prevalence in VLBW (<1.5kg) infants admitted to a South African NICU,[117] and 89% prevalence in LBW (<2.5kg) neonates at admission to a Nigerian NNU.[164] Other KMC trials have also documented high levels of hypothermia, with Nagai et al reporting 35% point prevalence with standard care for LBW neonates in an Indian NICU.[63] Thus, the rates of hypothermia in our cohort are at the higher end of the previously reported range from similar settings, although data comparability between studies is hindered by heterogeneity in the hypothermia case definition (Temperature <36.0^{o}C versus 36.5^{o}C), differences in measurement methods (core versus skin temperature) and inconsistent reporting of covariates between studies (e.g. gestational age, chronological age or weight).

The hyperthermia prevalence of ~10% in the eKMC trial cohort is similar to that reported from elsewhere in Africa. A larger study in Mozambique reported 10.2% (137/1344) hyperthermia prevalence in preterm neonates at admission and a non-linear (U-shaped) relationship between temperature and mortality, with highest mortality rates at the extremes of the temperature range.[114] Aetiology of poor thermal control in our cohort is likely multifactorial, with contributions from poorly functioning non-servo controlled incubators and radiant heaters as well as maternal and HCW behaviours around thermal control. The lack of servo-controlled incubators/radiant heaters at the trial site may have contributed towards either hypothermia or hyperthermia, as precise regulation of environmental temperature in response to neonatal temperature is essential for optimal thermal control. As described in other West African neonatal units,[120] over heating of radiant heaters was a frequent occurrence in our population, leading to increased risk of thermal stress. Lack of timely response to high incubator temperatures may have also contributed to the observed hyperthermia rates. Pathological causes of hyperthermia, such as fever in response to bacterial infection, are another possible aetiology of hyperthermia in our cohort, although we are unable to definitively ascertain the contribution of this as early onset infections were not rigorously investigated or defined in our participants. There was no between arm difference in hyperthermia prevalence rates, suggesting that skin-to-skin contact in an environment with high ambient temperatures is not associated with hyperthermia. The KMC trial participants all wore woollen hats, in recognition of the large surface area to volume ratio of the head and high risk of heat dispersion. Interestingly, the additional value of hat wearing as part of KMC is not proven, with an African multicentre clinical trial comparing KMC with or without a hat finding no between arm-difference in

mean time spent in normal temperature range.[165] This trial by Cavallin et al also demonstrated the high proportion (55%) of neonates with hypothermia during the first week after birth despite KMC provision, although adherence to KMC was variable in this study with no reported durations.[165] The identified association between baseline hypothermia and 28d mortality supports existing evidence that hypothermia plays an important role pathways to mortality for small and premature neonates. This association is well recognised,[166, 167] with a multicentre observational study (N=5277) in HIC estimating that the risk of mortality increases by 28% for every 1^{o}C drop in temperature for neonates 401 – 1499g old admitted directly from delivery room to NICU.[168] This observational study also identified an 11% increased risk of late-onset sepsis per 1^{o}C temperature decrease.[168] However, the causality of hypothermia in the pathway to mortality has not been fully established, with hypothermia being a possible consequence of more severe illness as opposed to a direct causation of mortality. However, it is imperative that maintaining a "warm chain" from delivery through-out the first day after birth and beyond is part of SSNC quality improvement initiatives to improve preterm outcomes.

7.5.3.3 Glycaemic dysregulation and linkage to mortality pathways

Hypoglycaemia occurred at one or more time point during the first 24h in one-fifth (20.9%, 58/277) of the eKMC trial cohort, with 6-hourly point prevalence of 4-10% (control) and 5-14% (intervention). Hyperglycaemia was more common than hypoglycaemia, with 33.6% (93/277) of all the cohort experiencing hyperglycaemic at one or more timepoint and 6-hourly point prevalence ranging from 8–14% (control) and 7–12% (intervention). This is consistent with a study of VLBW neonates admitted to a tertiary hospital in Nigeria, in which 31% were hyperglycaemic (glucose >7 mmol/L) between age 25-48h.[169] Independent risk factors for hyperglycaemia are well described for VLBW and preterm neonates managed on HIC NICUs[124, 170] but the evidence from LMIC settings is scanty. A small study from Nigeria reported that respiratory distress and probable sepsis were independent risk factors for hyperglycaemia, but important confounders were not included.[171] Hyperglycaemia has been linked to intravenous 10% dextrose fluid administration, [169] with conflicting evidence for the risk relative to dose of dextrose infusion.[124] Iatrogenic over-infusion of 10% dextrose maintenance fluids is a frequent occurrence at EFSTH and other similar low resource neonatal units,[169] due to absence of automated fluid pumps and reliance on burettes or fluid giving sets which require manual calculation of the number of drops per minute and close observation of fluid rates by nursing staff.

Our finding of an increased mortality risk with hyperglycaemia on univariate and multivariate regression is similar to other studies from varied settings, including HIC neonatal and paediatric intensive care units. The recent study by Okomo et al from EFSTH reported that hyperglycaemia at admission was associated with nearly twice the odds of inpatient mortality (n=601 term and preterm; OR 1.94, 95% CI 1.62 – 2.34, p =0.002).[27] A cross-sectional study in a Nigerian hospital also reported hyperglycaemia as a significant predictor of inpatient mortality (p=0.001).[171] It is not possible to infer a causal relationship between hyperglycaemia and mortality from our data, but our finding supports the importance of maintaining tight glycaemic control within normal range to improve neonatal outcomes and as a marker of quality of care. It should be noted that all glucose measurements in this study were from neonates who had been admitted for at least 10 hours (Chapter 6, Table 6-1) and had been receiving IV 10% dextrose fluids. Hence, we cannot comment on glycaemic control at time of admission, which may differ due to the absence of IV dextrose therapy

at this time. The role of hyperglycaemia within the preterm pathway to mortality warrants further exploration and could also be considered as a quality of care indicator in resource limited settings.

Interestingly, hypoglycaemia was not associated with mortality in the multivariate analysis of eKMC trial participants. This contrasts with a previous study from the trial site in which hypoglycaemia at admission was associated with a 1.6 increased odds of inpatient mortality.[27] A possible reason for the lack of association in our study is the relatively lower prevalence of hypoglycaemia in our cohort compared to rates of nearly 50% at baseline in the previous study, combined with our smaller sample size.

7.5.3.4 Cardiorespiratory stability as final common pathway to mortality

Abnormal heart rate (bradycardia or tachycardia) was a risk factor for mortality on univariate analysis and multivariate analysis but had relatively low prevalence (<5% in each treatment group). This most likely reflects that we had already excluded the most severely unstable neonates prior to recruitment and that most neonates had a heart rate within normal range. The association of abnormal heart rate with mortality reflects known physiological changes associated with critical illness and is consistent with the final common pathway to mortality, as outlined in figure 7-2.

Hypoxaemia was associated with all-cause 28-day mortality in our cohort, which is consistent with existing evidence that avoiding low blood oxygen levels is associated with improved outcomes.[133] This supports hypoxaemia as an important aspect of the final common pathway to mortality, as indicated in the conceptual framework (Fig.7-2).

Hyperoxaemia prevalence was very high in our cohort, with 99% of neonates being hyperoxaemic on at least 1 occasion during the first 24h of enrolment and 6-hourly point-prevalence rates of 65 – 76%. Nearly all (97%) of neonates received oxygen, either as supplemental low-flow oxygen or delivered via bCPAP, and prevalence of hypoxaemia was low (<5%). These findings suggest a lack of dynamic oxygen therapy titration in response to SpO_2 levels and highlight the potential for adverse outcomes such as ROP, in settings without high quality monitoring and oxygen delivery systems. Accurate titration of oxygen flow rates is challenging in settings without flow meters and adequate staffing to assess response to cessation of oxygen[172] and there is a substantial risk of oxygen “over-dose” in order to avoid hypoxaemia. Consistent with other low resource settings and international recommendations, decisions about starting/stopping oxygen therapy at the trial site were clinician led at once daily ward rounds[173] with ad-hoc reviews in event of clinical deterioration. Innovative methods to improve detection and maintenance of SpO_2 within target range are required to improve preterm and neonatal outcomes and raise the quality of SSNC. This should include pulse oximeters with improved ability to detect hyperoxaemia and with robust neonatal sensors and feasible power source, which is an important limitation to current pulse oximeter models. Improved HCW knowledge and understanding about oxygen toxicity and optimal SpO2 target ranges for preterm neonates is also required, in tandem with greater availability of flow metres to titrate low flow oxygen delivery. COVID-19 has highlighted the issue of oxygen production and supply chains across the world, yet more work needs to be done to ensure neonatal populations have access to appropriate and safe oxygen in the most resource limited settings.

We did not have access to ophthalmological or neurological investigations to evaluate the impact of abnormal oxygen levels within our cohort and long-term follow-up was beyond the scope of the trial. However, evaluating the neurodevelopmental outcomes for neonates <2000g is an important area for future research with a current paucity of weight-specific follow-up data from SSA for early childhood development outcomes during the first 5 years after birth.

7.5.3.5 Other risk factors for preterm mortality

7.5.3.5.1 Resuscitation at delivery

Resuscitation at delivery was associated with mortality on multivariate regression in our cohort, with nearly four times the odds of dying within 28 days compared to neonates not resuscitated (OR=3.98, 95% CI, 1.04 – 15.1.P=0.043). This may suggest a causative role for intra-partum related asphyxia (IRA) within the pathway to mortality for preterm neonates. Muhe et al, identified asphyxia as the primary cause of death in 14% of Ethiopian preterm deaths, with highest risk at 28 – 31 weeks' gestation, based on expert opinion and pathology assessments.[86] Apgar score <7 at 5 minutes has also been associated with mortality in West African settings[161] but is a subjective non-specific indicator of general condition at birth and often not recorded, as shown by our high rates of missing data (Chapter 6, eTable 1). Premature neonates may be resuscitated at delivery for several reasons, ranging from mild cyanosis or poor respiratory effort to apnoea and cardiac arrest. The normal neonatal oxygen saturation range in-utero is approximately 65% and physiological stabilisation immediately after delivery can take up-to 5 minutes, or longer for premature neonates, for the oxygen saturation level to reach "normal range" >88 – 90%. Thus, it is not uncommon for term and premature neonates to be cyanosed immediately after birth as part of their normal transition and to be given oxygen or resuscitation breaths unnecessarily. If IRA played a significant role in the pathway to mortality within our cohort, we would expect signs of NE, including seizures, within the first 24h after delivery, which we did not observe. Thus, we advise caution against over interpretation of our finding of an association between resuscitation at delivery and mortality, in the absence of more definitive radiological or pathology based NE diagnostic data. Understanding the prevalence and impact of IRA on preterm outcomes is an important area for future research.

7.5.3.5.2 Place & seasonality of birth

Birthplace (inborn/out-born) and mortality were not associated on univariate analysis. This is important as our cohort consisted of predominantly health-facility born neonates, with an equal mix of inborn (EFSTH tertiary maternity unit) and out-born (range of primary health centres, district hospitals and private clinics). This contrasts with existing evidence from West Africa indicating that birthplace is an important predictor, yet the direction of influence is complex with conflicting evidence. Outborn status was positively associated with mortality previously in The Gambia[27] and Ghana,[161, 162] possibly reflecting delayed care seeking or referral,[174] challenges in optimal neonatal transportation,[162] or differences in care available at different health facilities (e.g., antenatal steroids).[175] Conversely, inborn status was associated with early neonatal death in Nigeria[163] and may reflect the higher risk profile of neonates born to mothers requiring tertiary maternity care. Consistent with other Gambian studies, we did not identify rainy season admission as a risk factor for mortality.[176]

7.5.4 Aetiology & timing of neonatal inpatient mortality

Suspected and confirmed infections, particularly late onset, were an important cause of mortality in our cohort, responsible for over 50% of deaths and caused by MDR GNB in 70% (7/10) of confirmed infection cases. Previous *Burkholderia cepacia* and MDR-*Klebsiella pneumoniae* outbreaks at the trial site in 2015 and 2016 were genotypically linked to environmental sources, principally contaminated fluids and antibiotics.[79] Considering that we identified IV fluids contaminated with *Burkholderia cepacia* and *Pseudomonas spp*. at trial onset (Chapter 3) and temporal association with two neonates with invasive *Burkholderia cepacia* infection around the same time period, it is plausible that contaminated IV fluids were implicated in acquisition of late onset infections during the eKMC trial, although this requires detailed genomic analysis of invasive and environmental isolates to confirm. Perinatal septic risk factors were present in 29 – 36% of intervention/control participants, respectively (Chapter 6, eTable 6-1), yet were not associated with mortality in the exploratory analysis. In the absence of inflammatory (CRP/pro-calcitonin) or microbiological (blood/CSF culture) investigations and post-mortem data, infectious contributions to cause of death before 72h cannot be excluded and the extent of early onset infection in our cohort is not known. Nosocomial outbreaks on KMC units have previously been reported due to mycobacterium tuberculosis,[177] RSV,[178] and MRSA,[179] highlighting the importance of optimising IPC practices consistent with any health facility setting.

There were more deaths due to suspected RDS in the control arm (34% vs 14%) despite a similar risk profile (weight and gestational age) in both groups. However, caution in over interpretation of this is warranted, as reliable data on antenatal corticosteroid use was not available and there may have been confounding from different exposures to protective steroid exposure. The diagnosis of RDS in our cohort was based on review of clinical history and examination, with no chest X-rays to corroborate the diagnosis or exclusion of other co-morbidities. Despite these inconclusive observations about cause of death in the eKMC trial cohort, the role of RDS in the pathway to mortality is likely to be very important. This was demonstrated by the SIP study which identified RDS as primary cause of death in 45% (502/1109) of Ethiopian preterm neonates, using detailed post-mortem methods.[86]

7.5.5 Effect of early kangaroo mother care on physiological factors

7.5.5.1 Effect of early kangaroo mother care on thermal control

We identified no evidence for effect of early KMC on hypothermia or hyperthermia within the cohort of unstable neonates, except for sub-group analysis showing reduced hypothermia in neonates <1200g (Chapter 6). This contrasts with reports of 72% to 78% relative reduction in hypothermia associated with intermittent KMC in stabilised neonates.[48, 53] Nagai et al also reported non-significant differences in hypothermia (Temp<35.5^{o}C) with early KMC in a relatively unstable Indian population, but had very low rates of hypothermia within 48h (0/37 in eKMC; 2/36 in control).[63] Conversely, the iKMC trial reported evidence that immediate KMC started within 1h after birth and provided for median 16.9h/day reduces the relative risk of hypothermia by 35% (133/1602 (8.3%) in control; 90/1609 (5.6%) in intervention. RR 0.65, 95% CI 0.51 – 0.83).[64] A possible reason for our non-significant finding is the reduced fidelity of the intervention with relatively low KMC duration (discussed further in Chapter 8) and lack of linkage to whether the neonate was receiving KMC at time of temperature measurement. We found no evidence for effect of early KMC on risk of

hyperthermia, similar to the 2016 Cochrane review which reported a non-significant reduction with intermittent KMC from 4 RCTs including stable neonates (RR=0.79, 95% CI 0.59 0 1.05) and 1 RCT of relatively stable neonates (RR=1.05, 95% CI 0.56 – 1.99).[48] The effect of immediate KMC on hyperthermia was not reported by the iKMC study.[64]

7.5.5.2 Effect of early kangaroo mother care on glycaemic control

Evidence for effect of early KMC on glycaemic control (hypo or hyperglycaemia) was not found by this descriptive analysis. This contrasts with the systematic review by Boundy et al which identified that KMC was strongly protective against hypoglycaemia (RR=0.12, 95% CI 0.05 – 0.32).[53] However, of the two RCTs included in the Boundy et al meta-analysis, one reported no difference in episodes of hypoglycaemia between KMC and conventional care yet had very low rates of hypoglycaemia (0 cases in KMC group versus 1 case in standard care group), and hypoglycaemia was not pre-specified as a formal outcome measure.[180] The other trial conducted by Rao et al in India reported reduced risk of hypoglycaemia with KMC (4/103, 3.9% versus 36/103, 35%) but there was scant reported data on the baseline glucose levels and frequency of checking blood glucose levels in both groups.[181] The iKMC trial did not identify any effect of KMC on hypoglycaemia and had similar hypoglycaemia prevalence rates to our cohort (10% in both arms. RR 1.15, 95% CI 0.85 – 1.56).[64] During the early phase of the eKMC trial there were HCW concerns that KMC provision disrupted safe IV fluid administration due to blockage or disruption of the IV line by the KMC wrapper or baby's position. Considering blood glucose control as a proxy for IV fluid administration issues, our findings are reassuring that early KMC can be safely provided to unstable neonates alongside IV fluids.

7.5.5.3 Effect of early kangaroo mother care on cardiorespiratory stability

We observed no effect of early KMC on mean heart rate, proportion with bradycardia/tachycardia, proportion hypoxaemic/hyperoxaemic or median SpO2 levels. This is consistent with the eKMC trial findings that early KMC was not associated with improved stability as measured by the composite aSCRIP score (Table 6-2). Existing evidence from Boundy et al suggests KMC has a moderate effect on respiratory rate (n=12 studies, mean difference = 3 bpm, 95% CI -5.15 to -1.19) and oxygen saturation (n=14 studies, mean difference 0.9%, 95% CI 0.35 – 1.45) and no effect on heart rate (n=15 studies, mean difference 0.4 bpm, 95% CI -2.25 – 1.42). This evidence is derived mostly from observational or quasi-experimental studies with baseline parameters within normal range and small, clinically insignificant effect sizes.[53] Three studies from the Boundy review which were conducted in HIC NICUs included neonates on respiratory support, mostly CPAP[56, 182, 183] and all studies in low resource settings were conducted on stable neonates. The iKMC trial did not include stability indicators as an outcome but did report no evidence for difference in time to clinical stabilisation with KMC compared to standard care (73.8h versus 74.8h. RR 0.98, 95% CI 0.90 – 1.07).[64]

7.5.6 Strengths & limitations of exploratory mechanistic analyses

7.5.6.1 Strengths

These exploratory analyses provide valuable insights to the changes in mortality observed during the eKMC trial and a rigorous estimate of the mortality benefit from eKMC trial participation. The exploration of factors associated with mortality in our trial cohort gives insights to the trial population and underlines what is already known about preterm pathways to mortality and mortality risk factors, especially the importance of optimal thermal control. The large dataset for exploratory

analyses of physiological factors provides detailed understanding of thermal control, glycaemic control and SpO2 levels during the first 24h of enrolment with subsequent insights to the quality of care provided at the trial site.

7.5.6.2 Limitations

There were some significant limitations inherent to these exploratory analyses, as discussed below:

7.5.6.2.1 Cause of death attribution not reliable or rigorous

The reliability of the cause of death data from eKMC participants is limited due to the absence of verbal autopsy, lack of detailed investigations and post-mortem insights. The lack of reliable aetiological data informed our decision not to publish causes of death (Chapter 6) and limits our insights into the prevalence of RDS, NEC and IVH in our cohort. Multiple pathologies are common in neonates, especially with infections, and differentiation of death with infection as opposed to due to infection is needed via confirmation of invasive infections and linkage to causal pathway to mortality.

7.5.6.2.2 Non-specific diagnosis of suspected infection

The detection of suspected infections during the eKMC trial relied on a relatively non-specific clinical score to detect late-onset infections. The Rosenberg score had only 50% specificity compared to positive blood culture, as shown in the original validation study (n=500 preterm neonates with suspected nosocomial infection admitted to a Bangladeshi level 2 NNU).[11] This is consistent with limitations for other KMC trials assessing infection outcomes, which are discussed in more detail in Chapter 8. There are multiple proposed definitions of neonatal sepsis, mostly geared towards well-resourced settings including measurement of inflammatory biomarkers (CRP/FBC) or metabolic acidosis (pH/lactate). Previous efforts to define neonatal blood stream infections for use in international maternal vaccine trials proposed different levels of definitions according to capacity for laboratory investigations,[184] with level 3 criteria based on non-specific clinical signs of severe illness[185] similar to the adapted PSBI criteria used as a screening tool used in the eKMC trial. A recent case-control study in Thailand reported a 6-factor score with 88.5% sensitivity, 90.4% specificity and an area below Receiver Operating Characteristics (ROC) curve of 95.5% compared to culture confirmed late-onset neonatal infections, including preterm neonates. The score included the following parameters: poor feeding; abnormal heart rate (outside 100 – 180 bpm); abnormal temperature (outside 36 – 37.9^{o}C); abnormal SpO_2; abnormal leucocytes (per age criteria) and abnormal pH.[186] This pragmatic and validated score was published after the eKMC trial protocol was developed but is a viable option for future neonatal trials assessing late-onset infection outcomes.

7.5.6.2.3 Limitations to assessing vulnerable phenotypes

Admission weight was taken as a proxy for birth weight, due to the unreliability and inconsistency of birth weight measurements which would have been collected from multiple referral sites with no quality assurance. As all screened and recruited neonates were aged <24h at time of weight measurement, we do not expect this to differ substantially from the birth weight. We did not explore gestational age-specific differences in mortality and physiological factors and hence cannot comment on growth restriction as a mortality risk factor or examine the weight-for gestational age specific mortality rates. This would have added value to the analyses, as SGA and appropriately grown preterm neonates have different mortality risks.[34] Although use of published centile charts to

categorise participants as SGA could have been used (e.g., INTERGROWTH-21 charts), meaningful assignation of SGA relies on having accurate gestational age estimations, which we lacked. The gold standard pre-natal gestational age assessment is first trimester ultrasound, for which we did not have reliable or frequently available data during eKMC trial. There are over 18 postnatal gestational age assessment tools, of which Dubowitz score is the most accurate with accuracy +/-2 weeks compared to first trimester ultrasound.[158] However, Dubowitz tool is complex to administer with over 24 parameters. The New Ballard score, which we used in the eKMC trial is widely recognised as being simple to administer and is commonly used in neonatal trials yet has +/-4 week window compared to ultrasound.[158] Despite rigorous efforts to reduce interobserver variability during eKMC trial, the unreliability of this method is a limitation in reliably assigning gestational age and SGA categorisation. Development of accurate, feasible and affordable gestational age assessment tools for use in third trimester and postnatally are urgently needed both as research tools and for accurate clinical assessment and prognostication.

7.5.6.2.4 Limitations to data linkage of kangaroo mother care and physiological variables

Importantly, we were not able to determine whether KMC was delivered simultaneous to when physiological variables were measured. Combined with the relatively low duration of KMC contact delivered, this limits the interpretation of our data for the effect of early KMC on physiological factors. Previous studies exploring effect of skin-to-skin contact or KMC on temperature used a before-during-after design with continuous temperature, heart rate or SpO_2 measurement during each period and clearly recorded adherence to KMC or control.[182, 183, 187, 188] This design was out-with the scope of the original trial design, but would have provided more insightful data about relationship between being in KMC position and temperature and highlights a drawback of conducting secondary analyses for which the study was not originally designed.

7.5.6.2.5 Limitations to physiological data measurement and analysis

Mean heart rate, respiratory rate and peripheral oxygen saturation may not be the most clinically relevant physiological variable to understand the cardiorespiratory stability of preterm neonates. We were also unable to measure or report on measures of cardiovascular stability apart from heart rate with no data on heart rate variability, perfusion, blood pressure or to represent the complexity of cardiovascular stability. Lack of access to peripheral or (more accurate) invasive blood pressure monitoring is frequently encountered in RLS [189] and is a major limitation to adequate cardiovascular management of high risk neonates. The respiratory and heart rate are crude indicators of the respiratory and cardiac effort which a neonate is making to sustain tissue oxygenation and perfusion. Oxygen saturation gives insight into the amount of oxygen in circulating blood but does not indicate the degree of tissue oxygenation, which depends on oxygen delivery and oxygen consumption. Recent advances in neonatal stability measurement include efforts to quantify tissue oxygenation using Near-InfraRed Spectroscopy (NIRS) as a non-invasive method of continuously measuring tissue oxygenation and perfusion.[190] This gives information about dynamic changes in oxygen delivery and oxygen consumption by tissues including brain and peripheral muscle tissue and would have provided insights into end-organ, particularly cerebral oxygenation. NIRS has recently been used to explore the effect of KMC on cerebral oxygenation associated with painful procedures[55] and is an exciting research tool with potential to understand preterm stability and the physiological effects of newborn interventions.

The pathways to mortality for preterm neonates are complex, with multiple, interrelated factors contributing to preterm deaths, especially in resource limited settings where health systems constraints limit optimal monitoring and management. These mechanistic analyses focused on only a few selected variables and were unable to measure many other important physiological factors such as heart rate variability, cortisol and blood pressure. Considering individual physiological factors may not have accounted for clustering of the effects of multiple factors (e.g., inter-linkage of concomitant hypothermia and hypoglycaemia) and innovative studies and analytical methods are required to adequately address that level of complexity.

7.6. Summary of the mechanistic analyses findings

We demonstrated substantial reductions in neonatal mortality during the eKMC trial period, with the highest relative risk reduction associated with clinical trial implementation and participation. However, neonatal mortality at the site continued to be high with potentially modifiable factors such as suboptimal thermal control and hyperoxaemia suggesting that the quality of SSNC could be further improved. The pathway to mortality for preterm neonates is complex with multiple factors contributing to final cardiorespiratory instability. Optimal thermal and glycaemic control are critical components of the pathway, especially in the smallest and most immature neonates. Infections due to MDR-GNB were implicated in nearly half of all neonatal mortalities, but an infection detection gap and limited reliable cause of death data limits interpretation of this observation and reflects the need for improved standardised definitions and innovative diagnostic tools. These analyses did not identify evidence for effect of early KMC on thermal or glycaemic control, but this may have reflected limitations in the study design. Further research using innovative measures of stability and appropriate study designs is warranted in future studies exploring early KMC mechanisms.

Chapter 8 - Discussion

8.1. Scope of the chapter

In the preceding chapters, this thesis presented the detailed preparations necessary to implement and conduct a RCT investigating the effects of early KMC in unstable neonates <2000g in a resource-limited setting. This was followed by a description of the eKMC trial methods and findings for primary and secondary outcomes, as well as mechanistic analyses to explore pathways to mortality and effect of early KMC on physiological factors.

This chapter aims to consider the main PhD findings within the context of the existing published evidence in-order to determine the clinical and public health implications of the research from a programmatic and policy perspective along with highlighting important research gaps. I will also reflect on key pragmatic trial design, operationalisation, and ethical considerations which I encountered whilst conducting the eKMC trial as well as the strengths and limitations of the PhD as a whole. Recommendations for policy, programmes and future research will be presented in the final chapter focused on three themes: (1) Small and sick newborn care (SSNC); (2) KMC for stable neonates and (3) KMC prior to stability.

8.2. Main PhD findings

The main findings from this PhD are outlined in Table 8-1 and are summarised below.

My first PhD objective focused on preparing the trial site, understanding the feasibility of providing early KMC to unstable neonates and mitigating barriers to trial implementation An essential aspect of this was to understand the perceptions of Gambian female relatives of hospitalised neonates towards SSNC and KMC. A qualitative study identified that female relatives were willing to be involved in SSNC and would support mothers with KMC during hospital stay and post-discharge. These findings supported the inclusion of female relatives in eKMC trial procedures, especially for provision of the intervention with surrogate KMC providers playing a central role.

My second PhD objective was to investigate the survival and clinical effects of early KMC in mild-moderately unstable neonates. This was achieved through an individual RCT (n=279) at the only level 2/2+ neonatal unit in The Gambia. The trial did not demonstrate evidence for effect of early KMC on mortality, likely due to being underpowered and having reduced fidelity of the intervention, due to delivery of <10h/day duration of KMC. There was no evidence for differences in other clinical outcomes, including infections, except for reduced prevalence of hypothermia with early KMC for neonates <1200g. However, our findings did demonstrate substantial survival gains possible with implementation of higher quality SSNC and provided valuable safety and feasibility insights for use of early KMC with unstable neonates in a pragmatic research setting.

My third PhD objective was to explore the pathways to mortality for neonates <2000g, including understanding the changes to mortality during the eKMC trial. This identified an estimated 24% relative morality reduction for all neonates <2000g compared to pre-PhD mortality rates as well as a 29% relative risk reduction in mortality for mild-moderately unstable neonates <2000g participating in the eKMC trial. High prevalence of hypothermia and hyperoxaemia suggest that SSNC could be further strengthened. Pathways to mortality for neonates <2000g are complex, but admission

weight, early hypothermia, hyperglycaemia and hypoxaemia were associated with all-cause mortality in the eKMC trial cohort. Infections, especially MDR-GNB, also played an important role, with recognised limitations to infection detection methods. We identified no evidence for an effect of early KMC on thermal control, glycaemic control, or cardio-respiratory stability in unstable neonates <2000g but improved study designs, stability definitions and monitoring tools are required.

Table 8-1. PhD findings presented by PhD objective and chapter

PhD Obj.	Chapter/s	Main findings
1	3, 4 **To prepare the research site with mitigation of barriers to trial implementation**	- Contextual changes to care were needed for trial implementation, including KMC set-up and SSNC strengthening (shift from level 2 to level 2+ NNU) - High case fatality rates for target population - Absence of mothers during early phase of NNU admission is an important barrier for operationalisation of the trial and provision of the intervention - Female relatives are important stakeholders for SSNC, KMC and early KMC o Elder female relatives hold authority for newborn care decisions o Small newborns viewed differently with biomedical models of care acceptable o High levels of respect for HCW authority is an enabler for early KMC
2	5, 6 **To investigate effect of early KMC on survival & clinical outcomes for mild-moderately unstable neonates <2000g**	- No mortality effect or difference in time to death was seen with early KMC compared to standard care, - Small sample size limits ability to detect difference in primary outcome - Survival gains possible with implementation of higher quality recommended SSNC - Low fidelity of the intervention due to low KMC duration highlights challenges in KMC provision, with limitations to measurement methods - Infection prevention effects of KMC were inconclusive due to low power but the context of high HAI risk may influence intervention effect - Reduced risk of hypothermia with early KMC given to neonates <1200g - No evidence for effect of early KMC on weight gain, exclusive breast feeding or duration of stay, in context of limited nutritional support and early KMC provided by mothers or female relatives - Early KMC was not found to be unsafe with monitoring but more safety data from varied settings is required as one third stopped the intervention for clinical reasons
3	7 **To explore pathways to mortality & effect of early KMC on physiology of unstable neonates**	<u>Pathways to mortality</u> - 21% relative reduction in mortality for all neonates - 24% relative reduction in mortality for neonates <2000g - 29% relative risk reduction in mortality for neonates' part of eKMC trial - Mortality rates at the trial site unacceptably high despite survival gains - Suboptimal thermal control and high prevalence of hyperoxaemia in eKMC trial cohort, indicates quality of SSNC could be further strengthened - Neonatal death attribution is challenging without investigations and post-mortem data - Gestational age-specific cause of death attribution is limited by current gestational age assessment tools - Infections, especially late-onset and due to AMR bacteria, play an important role in mortality of neonates <2000g with a priority infection detection gap - Multiple, interlinked pathways to mortality occur for neonates <2000g with hypothermia, hypoxaemia, and weight <1200g associated with 28d mortality <u>Effect of early KMC on physiological factors in unstable neonates <2000g</u> - Cardio-respiratory stability is complex and heart rate, oxygen saturation and respiratory rate don't adequately reflect physiology or end tissue perfusion - No evidence for early KMC effect on thermal control, glycaemic control or cardio-respiratory stability, but improved study designs, stability definitions and monitoring tools are needed

8.3. Objective 1: To prepare the research site (Chapter 3) with mitigation of barriers to trial implementation (Chapter 4)

8.3.1 Contextual changes in care necessary for trial implementation

The preparation phase at the trial site improved quality of SSNC with guideline development and implementation, KMC set-up for stable newborns, formalisation and promotion of bCPAP and increased focus on infection prevention and detection of HAI (Chapter 3). This shifted the level of care from level 2 to level 2+, as per the WHO classification of hospital newborn care levels.[21] The health system barriers and enablers we encountered during KMC set-up mirror those reported elsewhere in Africa.[47] Sufficient space and supplies, with a dedicated space for KMC and provision of recreational activities were key enablers, central to our ability to establish KMC for stable newborns. Local leadership support through establishment of the KMC taskforce, development of KMC guidelines and supportive supervision with improved accountability through dedicated KMC registers were all facilitators for KMC implementation.[47] Despite the potential for challenges associated with external partners propelling momentum for KMC programmes, we were able to effect sustainable change through early and equitable involvement of GGMoH and third-sector (UNICEF The Gambia) partners with encouragement of local KMC champions to build momentum in practice.[62] This sustainable set-up of KMC is demonstrated by the Stages of Change progress monitoring tool results showing an increase from "creating awareness" at PhD onset (score=4) to "Integrate into routine care" (score=22) after 20 months, followed by sustained KMC provision (scores 24-25) by the end of the eKMC trial (Fig.3-4).

8.3.2 Female relatives are important kangaroo mother care stakeholders

Involvement of female relatives (aunts, grandmothers, great grandmothers) was identified as a potential mitigating strategy for trial recruitment and intervention delivery, yet perceptions of this key stakeholder group towards SSNC and KMC were previously under-represented in the literature.[51, 191] Thus, there was a need to obtain context-specific understanding of the feasibility of including Gambian female relatives as surrogate KMC providers and to gain broader insights into their perceptions towards SSNC and KMC.

We identified that female relatives, especially elder females, expect to be involved in SSNC, either as a support to the mother or as a substitute caregiver until the mother is available, with gendered roles and responsibilities underpinning their acceptance of being involved in SSNC. This is consistent with other African studies exploring the role of female relatives in provision of other child health interventions,[47, 192] especially in West Africa.[193, 194] Stress related to extended hospitalisation, including concerns about domestic and other childcare responsibilities, was the most frequently mentioned family-level barrier to KMC as identified by previous studies[47] and our own qualitative study with female relatives in The Gambia.[195] Family attitudes and beliefs are crucial for family buy-in and support to enable mothers to practise KMC. Since conduct of our qualitative study, a Malawian study of KMC caregivers, including grandmothers, reported similar findings to ours, highlighting the grandmother's role as a surrogate KMC provider, especially with twins, and in caring for both mother and baby.[192]

Gambian female relatives view KMC as a biomedical innovation, acceptable due to the belief that small and preterm neonates are exempt from traditional newborn care practices (Chapter 4). This

finding has positive implications for involvement of female relatives in the provision of early KMC for unstable neonates, as illustrated during the eKMC trial when nearly half of the intervention arm received initial KMC from female relatives (Table 6-4). There is limited published data exploring female relatives' perceptions of KMC in unstable neonates in African settings, as two previous studies involving unstable neonates focused on parental and HCW perceptions only.[153, 196] Considering the central role of female relatives in African newborn care, targeted research is required to understand their knowledge, perceptions, and attitudes towards using KMC prior to stability and this is an evidence gap to inform any future policy or programmatic change.

We also identified that respect for the authority of HCW is an enabling factor for Gambian female relative involvement, highlighting the importance of ensuring HCW understanding and acceptance of KMC in promoting maternal/family uptake. Educating antenatal and neonatal HCW with regular training is a critical aspect of KMC programmes,[197] and is even more critical for early KMC prior to stability, when major changes to NNU infrastructure and workflow are needed to facilitate continuous presence of families on NNUs and support safe KMC provision.

Financial costs were not mentioned by female relatives in our study, but have been identified as a key barrier for health facility KMC provision from other studies.[51] Financial pressures include loss of earnings from disrupted livelihoods,[192] transport costs for working mothers/relatives to attend the hospital,[51] provision of supplies and food[47] and costs of attending follow-up clinics (transport, loss of earnings etc.). Conversely, in settings where accommodation and food are provided for families and KMC enables earlier discharge, parents believe that KMC decreases the cost of hospital bills.[51] Detailed economic evaluations of facility-based KMC in African settings, including measures of cost-effectiveness and considering the costs to women, families, health system and society, is currently lacking yet is high priority.[48] Economic evaluations in South America reported cost-savings with KMC compared to incubator care for health facility or provider[198] and an Ethiopian analysis reported an incremental cost-effectiveness ratio of US$8 per disability-adjusted life year averted with a 20% increase in KMC coverage.[199] This a key area for future research especially from African settings where cost planning tools to enable implementation of KMC at scale are also urgently required.

8.3.3 Fathers' role within small and sick newborn care and kangaroo mother care

Fathers were identified by female relatives in our qualitative study as playing a limited direct role in SSNC and KMC due to their primary role as main breadwinner for the family and the gendered expectations for newborn care and KMC being the preserve of women (Table 4-1). This is a common finding from other African studies,[47] although a recent study in Malawi identified fathers and grandfathers as a critical link between home and facility, especially in arranging for a female family member to be present with the mother.[192] Other roles for the father within SSNC include providing essential supplies and food during hospital admission, being present during KMC counselling and offering emotional support to their partners both in hospital and post-discharge.[47]

During KMC implementation for stable neonates at the trial site, fathers did not routinely provide KMC due to concerns from HCW and other mothers about the impact of father's presence on women's privacy. During the eKMC trial, five fathers provided initial KMC for short periods to unstable neonates whilst waiting for the mother and when female relatives were unavailable

(Chapter 6). The eKMC team observed that mothers were uncomfortable exposing their bodies during breastfeeding or providing KMC in the presence of men on the NNU. This was also identified in Malawi, with fathers expressing unease linked to conceptualisation of the KMC ward as a female space.[192] This highlights a dichotomy as although Gambian men are not the main decision makers nor carers of newborns, they hold positions of power within families in patriarchal societies, hence father's acceptance and support for KMC, including KMC follow-up, is important for local and national scale-up. Further research into paternal perceptions of KMC for stable and unstable neonates is needed, with potential for greater participation through adaptation of other maternity health service delivery models which have successfully incorporated fathers, such as the PMTCT model.[200]

8.3.4 Family-centred care model to be incorporated within small and sick newborn care

Inclusion of female relatives and fathers in SSNC is important for promoting a family centred care (FCC) model in The Gambia and other similar settings. FCC is a philosophy of care developed in the 1990s from the Humane Neonatal Care Initiative,[201] based on a collaborative partnership between the family and clinical team in delivering health facility care to unwell neonates.[46] The guiding principles for FCC include: family participation in care; addressing the family's needs; collaboration, respect and dignity; and knowledge sharing between HCW and families.[202] FCC empowers parents by involving them in caregiving, promoting a beneficial partnership and respectful interactions between parents/families and HCWs with strengthening of parental skills in caring for their newborn. The FCC-model has the potential to improve outcomes for small and sick newborns by improving breastfeeding,[203] weight gain and enhancing caregiver competencies[202] which may translate to better newborn care post-discharge. The FCC model was first developed in HIC with a recent shift to apply the model to neonatal and childcare in LMIC settings,[202-204] yet there is scanty evidence for how to integrate FCC into SSNC in varied African contexts and limited consideration of how different family structures and power dynamics may influence adoption of this model (e.g., between families and HCW).

We incorporated several aspects of the FCC philosophy during KMC implementation as standard care at the research site (Chapter 3). This included promoting family participation in care during KMC, providing unrestricted access to neonates during admission, providing a respectful environment with WASH and recreational facilities as well as targeted job aids and training to assist HCW in respectful communication with families. This was more formalised during the implementation of early KMC for unstable neonates, when we used a formal checklist approach to educate parents/female relatives about possible danger signs, observation of IV fluid drip rates, avoidance of blocked or kinked IV lines and monitoring of pulse oximeter alarms. This level of caregiving provided by KMC providers to unstable neonates goes beyond the FCC-model and is more consistent with the family-integrated-care (FIC) model, recently described in HIC and placing mothers/family members at the centre of care with more practical responsibilities for newborn care.[205] Promoting the FIC model in resource limited settings could formalise the often informal task-shifting of nursing duties onto mothers/families which takes place on busy resource limited NNUs, and help promote better supervision of mothers/families in carrying out newborn cares such as supplemental feeding. The Mother-NICUs established during the iKMC trial also exemplify a FIC-model with mothers playing an active role in hospital management of small and sick newborns.[64] This expansion of FCC to a more

FIC model of care should be explored further within LMICs, especially if there is a policy shift towards starting KMC earlier for unstable neonates.

8.3.5 Summary of discussion for objective 1

In summary, substantial improvements to SSNC were required in-order to prepare for the eKMC clinical trial, which contributed to provision of higher quality and more family centred SSNC at the trial site. We identified that female relatives of small and sick newborns are key stakeholders for provision of SSNC, including KMC, in The Gambia. The acceptability and feasibility of providing FCC and FIC models of care for small and sick newborns in LMICs is a current evidence gap and requires consideration of all family members for both future implementation policy and research.

8.4. Objective 2: Clinical trial to investigate the effect of early kangaroo mother care on neonatal mortality and morbidity (Chapters 5 & 6)

8.4.1 eKMC trial findings in the context of other evidence

The eKMC trial was conducted over 22 months from 2018 to 2020 at the only level 2/2+ neonatal unit in The Gambia as a non-blinded individually randomised clinical trial, involving 279 mild-moderately unstable neonates weighing <2000g and aged <24h at screening. The primary outcome was all-cause mortality within 28 days with secondary outcomes to explore important morbidities and mechanisms of effect. The eKMC trial did not detect any evidence of a between-arm difference in mortality or time to death (section 8.4.2). This contrast with the iKMC trial findings of a 25% mortality reduction for neonates 1000 to <1800g, reported since eKMC trial closure.[64] There are two important reasons why we cannot draw definitive conclusions from the eKMC trial about the mortality effect of the intervention:

(1) Despite being adequately powered at trial onset, there was insufficient sample size at trial end to detect a difference in primary outcome, due to halving of control arm mortality during the trial period and recruitment challenges.

(2) We demonstrated that early KMC provision to unstable neonates is feasible, but the intervention had low fidelity due to KMC duration <10h/day, which may have influenced the trial outcomes. The reasons for not achieving longer daily duration of KMC are multifactorial and will be considered in relation to other studies, especially the iKMC trial which achieved >16h/d duration in the intervention arm.[64] There were also limitations to measurement of KMC duration during the eKMC trial and an overall evidence gap for KMC measurement methods and tools.

We did not identify evidence for any beneficial effects of early KMC on other secondary outcomes, except for reduced prevalence of hypothermia in the sub-group of neonates <1200g.[206] We also did not identify any safety concerns with the intervention in the context of continuous monitoring in a research setting. These findings will be discussed in detail in relation to evidence from the iKMC trial and other studies investigating KMC effect and safety in stable neonates (section 8.4.4).

8.4.2 Effect of early kangaroo mother care on mortality

Our lack of evidence for a mortality effect contrasts with the findings from the recently published multi-centre iKMC trial which reported a 25% relative reduction in 28d mortality with immediate (<1hr after delivery) KMC provided to singleton and twin neonates 1000 to <1800g. The number needed to treat to prevent one death was 27 (95% CI 17 – 77) and the trial was stopped early by the

DSMB due to the positive finding at interim analysis.[64] It is worth exploring the iKMC trial in more depth to understand the varying settings, population and other treatments received compared to the eKMC trial.

The iKMC trial was conducted at four African (Ghana, Nigeria, Malawi, Tanzania) and one Indian site, all providing level 3 neonatal care (Table 1-1). The 28-day mortality rates in the control arm ranged from 10.8% in Ghana to 23.6% in Malawi with only the Malawian site having a comparable inpatient mortality rate to the Gambian eKMC site (24%). A higher level of newborn care was available to both arms at iKMC sites, with respiratory support including bCPAP and mechanical ventilation/surfactant (Indian site only).[64] This contrasts with the eKMC site which had only low-flow oxygen and bCPAP available and this disparity may have contributed towards the difference in mortality rates and intervention effect between the trials. There are also possible differences in the quality of standard care provided in the two trials, with only 8.3% of the iKMC control arm being hypothermic (temperature <36.0^{o}C as defined in iKMC trial) between 2h after randomisation to hospital discharge compared to 34% - 45% of the eKMC control arm at each 6-hourly time point during the first 24h of enrolment (Table 7-6). Substantial HCW training at the iKMC trial sites was also conducted to upgrade the quality of SSNC prior to trial onset.[64]

Although not powered to detect a 28d mortality difference by trial site, the iKMC sub-group analysis of identified a 34% relative reduction at the Indian site (RR 0.66, 95% CI 0.5 – 0.89), where 43% of participants were recruited. The effect size from the combined African sites is smaller at 17% (RR 0.83, 95% CI 0.66-1.04) with the site in Ghana not showing any evidence of mortality effect (RR 1.13, 95% CI 0.66 – 1.95) and the Nigerian site showing the smallest effect size with confidence intervals crossing 1 (RR 0.84, 95% CI 0.39 – 1.79). This possibly reflects the smaller sample sizes and lower control arm mortality rates in Ghana (n=409;10.8%) and Nigeria (n=215;12.2%). However, the possibility of a heterogeneous effect of the intervention in different geographical and health-care settings cannot be excluded as there is no published data detailing differences in SSNC availability, quality or delivery at each iKMC site. There were also differences in trial set up between the iKMC sites, with the intervention arm managed in a separate mother-NICU at two sites as opposed to a combined NICU/Mother-NICU at three sites.[64] This important variation may have introduced performance bias in other aspects of SSNC provided to iKMC trial participants, especially in the domain of IPC.

These differences in context of care are important to consider, as KMC works in combination, not isolation, with other SSNC, particularly respiratory support. For example, a neonate with moderate-severe RDS will require respiratory support to survive and if that is not provided, KMC is likely to have a limited effect on prognosis. However, if the newborn is already receiving optimal respiratory support, being held in KMC position simultaneously may optimise thermal control, promote stability through neuro-endocrine mechanisms and contribute towards survival. As the eKMC participants did not simultaneously receive bCPAP and KMC, we should consider our intervention to be different to that provided in the iKMC trial when bCPAP and KMC were administered together.

Immediate KMC had similar effects across the categories of birth weight, gestational age, weight for gestational age, type of delivery and singleton/twin status, based on sub-group analysis. Although detailed interpretation of the precise effect sizes in the sub-group analysis is limited by lack of

adjustment for multiplicity, there is a trend in reducing effect size with smaller weight and gestation neonates. Neonates weighing 1.5 to <1.8kg had 28% reduced risk of 28d-mortality (6.8% vs 9.5%; RR 0.72, 95% CI 0.52 – 0.98) compared to 16% reduced risk for neonates 1 to <1.2kg (28.8% vs 34.6%; RR 0.84, 95% CI 0.63 – 1.13).[64] As discussed in chapter 7, it is plausible that different sub-groups of small and sick newborns will have different mortality risks and pathways to mortality. As neonates <1 kg were excluded from the iKMC trial and comprised only 11% (31/279) of the eKMC cohort, further research into the effectiveness of KMC in the lower gestational age and weight categories remains a priority evidence gap due to the higher mortality and morbidity risk in that population.

Baseline stability and treatments received before enrolment were not published with the iKMC trial primary results. Neonates were excluded at trial entry if they did not breath spontaneously within 60 minutes, but the proportion requiring ventilation, bCPAP and oxygen at enrolment are not described.[64] This limits direct comparison with our findings from the eKMC trial as well as restricting understanding of which sub-population of neonates 1000 – 1799g will benefit from immediate KMC. Direct comparison of the eKMC and iKMC populations using standardised stability criteria would give more insights and enable pooling of data in meta-analyses. Stratifying by stability status is also important to enable clinical prioritisation of infants most likely to benefit from the intervention, as the demand for immediate KMC is likely to be greater than the capacity to provide it, if recommended by global policy.

Other medical management was provided to all iKMC participants according to the WHO minimum-care package for small infants[64] but concomitant medications/interventions received by each arm were not published with the trial findings.[64] Thus it is not possible to assess whether there were any between-arm differences in management which may have also influenced outcomes, such as use of respiratory support, antibiotics, or prophylactic caffeine. The iKMC trial made good efforts to reduce detection bias with an independent and blinded team assessing outcomes but the medical and nursing personnel providing actual care to the participants were not blinded to allocation arm. As we observed during the eKMC trial implementation, there is considerable potential for sub-conscious bias or therapeutic misconception as KMC is already an accepted and valued intervention. Hence, ensuring all other treatments are comparable between arms and being transparent about any imbalances is critical to identify any performance bias. This is a strength of the eKMC trial and, apart from an imbalance in the type of second line antibiotics used, there were no differences in other domains of SSNC, as shown by comparable concomitant treatments in both arms.[206] This may be more complex with a multi-centre trial as differences in standard care may exist between sites, but a site-specific report of concomitant medications/interventions from the iKMC trial would add value and enable direct comparison of participants between trials, especially for the iKMC sites in which separate Mother-NICUs were established.

Time to death was not significantly different with early KMC (4.1d in control; 3.8d in intervention. HR 0.83, 95% CI 0.5 – 1.35, Table 6-2), but our interpretation of this is limited due to having small sample size for this outcome as a result of substantial reductions to mortality in the control arm.[206] The iKMC trial did not include time to death as an outcome but observed a similar effect size in mortality reduction at 72h (RR 0.77, 95% CI 0.58 – 1.04) compared to 28d (RR 0.75, 95% CI 0.64 – 0.89). The relatively lower event rates at 72h (5.8% in control at 72h versus 15.7% in control at 28d) indicate

that most deaths occurred between 72h and 28d,[64] but more granular detail on time of death is required for further insights into effect of immediate KMC.

8.4.3 Understanding the eKMC trial primary outcome

Two factors influenced why our eKMC trial primary outcome did not show evidence of an effect with early KMC: (1) Sample size was insufficient to detect a difference in primary outcome (2) Low fidelity of KMC delivered. Each of these will be considered in detail below.

8.4.3.1 Insufficient sample size to detect a difference in primary outcome

At trial onset the target sample size was 392, which was calculated apriori to provide 80% power (alpha=0.05) to detect a 30% reduction in mortality (48% to 36%). Mortality in the control arm was estimated at 48% based on feasibility study data (Chapter 3; 56% CFR) which was adjusted for an expected reduction in mortality due to trial implementation activities (15% relative reduction from 56% to 48%). This was consistent with published audit data collected from 2010 – 2014 which reported 48% CFR for all neonates <2000g.[27] The target effect size was based on the known effect size for KMC in stable neonates (40%),[48] with reduction to 30% considered a realistic between-arm difference. Considering the iKMC trial finding of a 25% effect size, we can reflect that this was an appropriate assumption. However, the control arm CFR was half of the pre-trial estimated rate and recruitment challenges limited participant numbers to only 279. Both of these factors contributed to the inability to draw definitive conclusions from the trial regarding the effect of the intervention on primary outcome and are explored in more detail below. It is worth noting that based on the actual control arm CFR (24%), n=1444 participants would have been required to detect a 25% reduction in 28d mortality (80% power, alpha=0.05).

8.4.3.1.1 Halving of mortality in the eKMC trial control arm

There are three possible explanations for the observed halving of in-patient mortality in our trial cohort compared to the pre-trial estimates used in the sample size calculation.

8.4.3.1.1.1 Improved quality of small and sick newborn care at eKMC trial site

The inpatient CFR for all neonates <2000g reduced from 47.7% (2010-2014)[27] to 36.1% (2018-2020), a 24% relative reduction (Chapter 7). Although we cannot definitively conclude causation, it is highly likely that improvements to SSNC during the trial preparation period contributed towards this mortality reduction. PhD related activities which may have raised the standard and quality of SSNC include: Implementation of a SSNC guideline with linked HCW training; introduction and standardisation of bCPAP use; implementation of KMC as standard care for stable neonates <2000g and enhanced, consistent focus on IPC (Chapter 3). Measuring the exact impact of individual components of higher quality SSNC on mortality rates at the trial site is challenging, but there is a strong individual evidence base for mortality reduction with KMC alone,[48] bCPAP alone[78] with a combined effect of multiple interventions likely to have the greatest impact.[89] A modelling study estimated that provision of WHO-recommended interventions could have saved the lives of nearly 300,000 preterm neonates in SSA in 2015. This study identified that comprehensive care for RDS was the most effective combined intervention to prevent preterm mortality, with oxygen/CPAP provision the most effective single intervention, resulting in 42,3000 lives saved.[89] The greatest impact was found with a model combining universal health coverage of hospital delivery, access to antenatal corticosteroids (with use as per WHO criteria), improved diagnosis of RDS and management with

surfactant and oxygen/CPAP, resulting in potential >190,000 lives saved.[89] Comprehensive thermal care for LBW neonates, including KMC in all settings, was estimated to prevent nearly 190,000 deaths, closely followed by universal access to prompt antibiotics for suspected sepsis (180,300 lives saved), breastfeeding (168,200 lives saved) and recommended hygienic cord care (159,900 lives saved).[89]

Estimating the mortality impact of implementing standardised guidelines is also challenging and is not addressed in existing global modelling estimates, which focus on a restricted number of interventions without consideration of wider improvements to monitoring, prescribing practice or whether appropriate interventions are provided (e.g., over-use of antibiotics, inappropriate use of caffeine in term growth restricted neonates). The changes to SSNC which resulted from implementation of the standardised SSNC guideline ranged from training clinicians in the New Ballard gestational age assessment score, to active changes in medication prescribing practices, management of glycaemic dysregulation and more standardised antibiotic regimes. An example is the use of aminophylline as second line prophylaxis for apnoea of prematurity. During the early eKMC trial phase there was a fatal-SAE of an eKMC participant and during the safety reporting and review process it was detected that incorrect aminophylline dosing was standard practice at the trial site with high risk of toxicity and potential to cause cardiac arrhythmias. Further scrutiny and case-note review of all inpatients during the preceding month revealed systematic errors in aminophylline prescribing, despite correct dosing in the standardised SSNC guideline. Appropriate action was taken with immediate trial site staff re-training and changes to prescribing practice with no further instances of aminophylline overdose detected in the eKMC trial population. This likely improved the quality of care for all neonates receiving aminophylline at the site, but quantifying the impact is complicated and not possible within the confines of this PhD. The recent publication of WHO standards for improving quality of SSNC[22] will help to fill this gap and enable future research to estimate the impact of higher quality care using standardised coverage targets for a wider range of care domains.

8.4.3.1.1.2 Mortality benefits from clinical trial participation

eKMC trial participants had a 29% reduced relative risk of dying before discharge compared to clinically comparable neonates managed on the same NNU over the same period (Chapter 7). This underlines the potential for direct clinical benefits associated with trial participation regardless of the intervention effect. This is particularly striking in high-mortality settings where the potential for improvements in outcomes are greatest. Along with the scientific and ethical need to evaluate interventions which address local health needs, this finding demonstrates and quantifies the tangible health benefits for clinical trial participants. Access to improved health care is an important extrinsic motivator for patients and families in their decision to participate in clinical trials,[207, 208] yet evidence to quantify the actual mortality and health benefits from trial participation is limited.

This observed “healthy effect” of the trial also enables exploration of the differences in care between recruited versus non-recruited neonates, which may provide insights as to how SSNC can be improved for survival benefit. A major difference was the closer clinical monitoring provided to all eKMC trial participants compared to non-recruited neonates. eKMC trial neonates received continuous pulse oximetry whilst receiving oxygen and until they were stable as per protocol definitions (Chapter 5). This was unavailable for non-recruited neonates due to limitations in the

number of functioning pulse oximeters, with spot checks of heart rate and SpO_2 conducted only once during the daily ward round and then as determined by clinical need. More intense monitoring is central to higher quality neonatal care, recommended by WHO and critical for early detection of deterioration.[172] There were also higher nursing to neonate ratios, with maximum 10 eKMC trial participants admitted simultaneously and minimum 1 research nurse and 1 doctor involved in their care in addition to hospital personnel. This contrasts with the 1:20 nursing to patient ratios for non-trial neonates. Nursing workforce shortages significantly undermine quality of newborn care and patient safety[209] and the more intense nursing care provided to eKMC participants is possibly contributed to improved outcomes. There was also more detailed scrutiny of the clinical condition and care provided to eKMC trial participants, especially during the first 24h of enrolment when participants were assessed 6 hourly. This was to ensure protocol and guideline compliance and to avoid performance bias as well as to detect adverse events, but a positive collateral effect was a greater focus on correct medication dosing and duration, appropriate IV fluid regimens and early detection of clinical changes. This included assessment and investigation of clinical deterioration, with a research clinician available 24h/d exclusively for trial participants. There was no established process for auditing compliance to the SSNC guideline in the non-trial population, so direct comparisons of quality of care are not possible to confirm this observation. Detailed and contemporaneous review of all SAEs were conducted by the PI and LSM as part of trial safety reporting procedures and this process also highlighted quality of care issues which were addressed in real time (e.g., prescribing errors) and may have also contributed to better participant outcomes. Access to blood cultures and other investigations at MRCG laboratories were an additional benefit for trial participants, along with routine medications provided free of charge and re-imbursement of transport costs if the neonate required assessment or follow-up post-discharge.

8.4.3.1.1.3 Over-estimation of mortality in the control arm

The eKMC trial sample size calculation was based on locally derived feasibility study data with 56% inpatient CFR for neonates <2000g meeting the protocol definition of mild-moderate instability (Chapter 3). However, this was a small sample size (n=36), with data collected over a short observational period (3 months) during the quieter dry season (Chapter 3). A larger dataset collected over a longer period (2010 – 2014) indicated 48% inpatient CFR for all neonates <2000g,[27] including those who were severely unwell or died during the initial admission period. Thus, it is possible that the feasibility study over-estimated the baseline CFR for mild-moderately unstable neonates <2000g. This highlights the importance of careful pre-trial planning for calculation of the sample size, with use of pilot studies and simulation modelling to consider the effect of uncertainty around key inputs such as the control arm outcomes.

8.4.3.1.2 Smaller sample size compared to intended target

We experienced challenges in attaining the target sample size of 392, with only 71% (279/392) of the target sample size enrolled. Key reasons included the limited number of trial beds at the site, absence of caregivers willing to provide the intervention and early cessation of the trial due to the COVID-19 pandemic. I will reflect further on the eKMC trial recruitment challenges and mitigating actions in section 8.6.2.

8.4.3.2 Fidelity of intervention delivered to mild-moderately unstable neonates <2000g

The fidelity of an intervention is defined as "the degree to which an intervention or programme is delivered as intended".[210] It is important to measure within programme or intervention evaluations as the fidelity affects how well the intervention succeeds. If the fidelity is low, this may result in a negative outcome result which does not reflect the true potential of the intervention had it been fully implemented (termed Type III error).[211] The intervention in the eKMC trial was defined as "continuous skin-to-skin contact between neonate and caregiver started within 24h of admission…advised for as long as possible, aiming for ≥18h/day". Hence, the fidelity of early KMC consists of adherence to (1) timing of first skin-to-skin/KMC contact and (2) Daily duration of KMC contact provided. Both these factors are considered below in the light of other trials with discussion of possible reasons for low fidelity and how the fidelity may have influenced the eKMC trial findings. Limitations in KMC duration measurement are also important to consider, as this impacts on the reliability of the fidelity data. The effect of the intervention is likely to be influenced by both timing of KMC onset and duration plus other aspects of this complex intervention such as the KMC provider (maternal or non-maternal). However, as the KMC provider was not pre-specified in the eKMC trial protocol I will not consider this as part of the fidelity, and it is discussed later in this chapter in relation to feeding and growth outcomes (section 8.4.4.2).

8.4.3.2.1 Timing of skin-to-skin onset

High fidelity for timing of skin-to-skin onset was achieved, with 86% (119/138) of the intervention arm starting skin-to-skin contact within 24h of admission, at median age 15.2h (IQR 10.7 – 22.0) and median time from admission 12h (IQR 7.4 – 17.9).[206]

A total of four neonates did not adhere to the intervention as outlined in the protocol, as they commenced KMC at >24h after admission or not at all. Two neonates deteriorated between screening and baseline assessment and met criteria for severe instability and "stopping criteria". One neonate was unable to start KMC within 24h of admission as no trial bed was immediately available. Another participant had an initially willing caregiver, hence was recruited, but the caregiver then had to attend to other duties and was unable to stay with the neonate. Both of these participants received KMC at a later time during admission. In addition, 13 twin participants were recruited and randomised to the intervention arm, but due to KMC provider preference to administer skin-to-skin contact to one neonate at a time, there was a delay in starting early KMC for one of the twin partners. However, these twins were still considered to be adherent to the intervention, as this is an inherent limitation for twins in a pragmatic setting and was not pre-specified as adherent in the eKMC trial protocol.

These findings demonstrate that starting KMC in unstable neonates who are also receiving oxygen and IV fluids within 24h after admission is feasible on a resource limited NNU. The time taken to establish unstable neonates in KMC position was artificially prolonged during the trial, due to the need for screening, consent, and baseline assessments. Hence, the time to first KMC contact in a clinical setting is likely to be quicker than we observed. During implementation of the eKMC trial intervention we observed the following important barriers to early onset of skin-to-skin contact following admission: Unavailability of a willing KMC provider and need for buy-in or permission from key decision makers within the extended family (father and/or elder female); reluctance of caregivers and HCW to provide early KMC to twins simultaneously; and HCW lack of confidence with

the practice, especially for more severely unstable neonates or those requiring multiple other medical interventions. These factors are explored further in section 8.4.3.2.2 and in-depth qualitative studies are warranted to identify barriers and enablers more rigorously, from a range of stake-holder perspectives including parents, female relatives and HCW.

There was no published evidence for optimal age at skin-to-skin initiation when this PhD started. I chose to focus on the first 24h after admission as a pragmatic choice in recognition of the high prevalence of out-born babies who may also potentially benefit from the intervention. The iKMC trial aimed to start KMC contact within 1h after delivery and achieved 1.3h (IQR 0.8 – 2.7).[64] Although we had high fidelity for this aspect of the intervention, it is plausible that the optimal window of opportunity for maximum mortality effect associated with KMC is "as early as possible", and that starting it later risks worse outcomes due to prolonged poor thermal control, metabolic acidosis, and respiratory compromise (Chapter 7). The ongoing OMWaNA trial defines the intervention as starting as soon as possible within 48h of admission and will provide further insights.

8.4.3.2.2 Daily duration of skin-to-skin contact

The fidelity of the daily duration of skin-to-skin (KMC) contact in the eKMC intervention arm was low, with median 6.7h/admission day compared to the target of ≥18h/d. This is in stark contrast to the iKMC adherence of 16.9h/d whilst on the Mother-NICU[64] and possibly contributed towards our non-significant mortality finding. This topic is briefly mentioned in the published eKMC trial article (Chapter 6) but is worth exploring in more detail, especially to discuss the possible reasons for low daily duration.

The longest duration of skin-to-skin contact in our intervention arm was on day one (8.9h/d, IQR 5.4 – 11.7), with a trend in reducing duration there-after, including after neonates had reached full stability and were admitted to the KMC unit (Table 6-4). This contrasts with findings from the OMWaNA feasibility study, which although had similar overall daily durations (median ranged from 4.5 to 9.7h/d) they reported lower KMC duration earlier in the admission period (mean 4.5h/d on first day of enrolment, n=12) and a slight upward trend over time.[153] iKMC reported consistently high KMC duration for the intervention participants during Mother-NICU admission (median 16.9h/d) and even higher on the KMC ward (20.2h/d).[64] Only 11% (15/138) of the eKMC trial intervention participants spent >10h/d in KMC position over the total enrolment period. This is substantially less than 85% (1353/1596) of iKMC trial intervention participants who had duration >10h/d during the first 72h after birth.[64]

There are several possible reasons why we achieved lower durations of KMC contact during the eKMC trial, including factors relating to the newborn, KMC provider and HCW/health system. We also identified low duration in KMC position for the control arm, reflecting wider, known, challenges in enabling prolonged KMC contact for stable newborns as well as challenges in accurate measurement of KMC duration. These will be considered in turn below:

8.4.3.2.2.1 Newborn factors affecting daily duration of skin-to-skin contact

Twins formed a substantial proportion of the eKMC trial population, with 30% of all participants born following a multiple gestation pregnancy and 17% being twin dyads who were both enrolled. The

eKMC trial twin population was heterogeneous, consisting of three distinct groups depending on their outcome and recruitment status:

a) Neonates born following a multiple pregnancy with one twin recruited and the other twin admitted to the NNU receiving usual care
b) Neonates born following a multiple pregnancy with one twin recruited and the other twin not present due to prior mortality or admission at another health facility
c) Both twins recruited to the eKMC trial and receiving either standard care or the intervention

Twin participants in these three groups may have experienced the intervention differently due to variations in where each twin partner was managed on the NNU and the ability of the KMC provider to do KMC simultaneously with both twins. Twin dyads with only one recruited neonate were managed in separate areas of the NNU due to limited incubator and radiant heater availability in the eKMC trial area. The non-recruited twin was managed in the main NNU as per usual care and the mother/carer was expected to feed and care for both twins. Hence, caregiver availability for provision of the intervention to the recruited twin may have been reduced compared to singleton participants. Twin dyads with one twin not available due to death or admission at another health facility could receive the intervention comparable to singletons yet had increased risk of mortality arising from the multiple gestation pregnancy. For twin participants allocated to the intervention arm, major factors limiting KMC duration was reluctance of KMC providers and HCW to place both twins into KMC position simultaneously and the restricted number of trial beds which precluded separate KMC providers for each twin. In this situation, KMC providers were encouraged to alternate skin-to-skin contact between each twin partner at 6 hourly intervals, in-order to standardise intervention delivery to twins. Another important reason for low KMC duration relevant to twin participants is the impact of being a twin on feeding and expression of breast milk, which by necessity, takes longer for twins. There was no option for safe storage of expressed breast milk on the NNU, so mothers had to express breast milk prior to each feed, further reducing the time available to spend in KMC position, especially for twins. Interestingly, iKMC had a similar proportion of twin pairs in the intervention arm (17%, 278/1609) and yet still achieved high fidelity for KMC duration.[64] More detailed insights into the effect of twin pairs (enrolled & not enrolled) on duration and quality of early KMC in unstable neonates is required, both from planned secondary analyses of eKMC trial data, iKMC implementation data and future OMWaNA trial insights.

Skin-to-skin contact was temporarily stopped in one-third of intervention neonates, most commonly due to being critically unwell and needing resuscitation, bCPAP or phototherapy. Although nearly half (22/46, 48%) of these neonates re-started KMC once stable, this may have also contributed to the low KMC duration delivered. If immediate KMC is incorporated in global SSNC policy there is an urgent need for implementation research to guide safe delivery of KMC to unstable neonates alongside other medical interventions, especially for bCPAP and phototherapy.

Other neonatal factors interrupting early skin-to-skin contact included medical procedures such as insertion of gastric tubes, re-siting of oxygen or peripheral venous cannula and routine cares such as cleaning, changing nappy or feeding. Ideally, breast feeding, and gastric tube feeding would be provided whilst in KMC position,[6] but supplemental feeds with cups, spoons or paladi may require the neonate to be removed from KMC position. The standard feeding practice for mothers at the eKMC trial site was to remove the baby from KMC position to express milk then attempt to

breastfeed with the expressed milk given via naso-gastric tube (NGT) feeds or cup before placing the neonate back into KMC position. This practice may have increased the time spent out of KMC compared to feeding via NGT whilst in KMC position. The OMWaNA feasibility study reported that the number of concurrent neonatal medical therapies (e.g., bCPAP, oxygen) did not affect duration in KMC position,[153] but more evidence to confirm this is warranted considering the small sample size.

8.4.3.2.2.2 Caregiver factors affecting daily duration of skin-to-skin contact

Caregiver reasons for interrupting KMC sessions during the eKMC trial included the need to rest, pray, eat, bathe, or perform chores such as laundry. Absence of a KMC provider due to illness or unwillingness to provide continuous KMC (once recruited) was not an important reason for reverting to standard care, except for one mother with a widespread rash (Table 6-4). However, we observed that mothers became tired and uncomfortable whilst practising KMC for long periods and required frequent reminders by HCW. This is similar to findings by Morgan et al who conducted 10 in-depth interviews with parents during the OMWaNA feasibility study and identified that inadequate education of KMC providers and difficulties in motivating mothers to practise KMC were important barriers to achieving prolonged KMC duration.[153] A time-motion analysis of 68 mother-newborn dyads on an Indian level 3 NNU based on 24h-recall data reported that the most common KMC provider reasons for interrupting KMC sessions with unwell neonates were to sleep, breastfeed and to meet visiting relatives. [212] As this Indian study highlights, the socio-cultural expectations around greeting and hosting visitors whilst in hospital should also be considered and are potentially amenable to community engagement activities and sensitisation.

At present there is limited data from the iKMC trial about how prolonged KMC durations were achieved, but establishment of Mother-NICUs is likely to have played an important role. Mothers were expected to stay with their newborns for 24h/day and to identify one or two helpers at enrolment.[64] Thus it is possible that only highly motivated mothers and families were recruited to the iKMC trial with a self-selecting population not representative of the general maternal population. Understanding and addressing maternal medical and mental health needs is also important and the iKMC trial included close liaison with obstetric teams for routine maternal checks and management of maternal illness/complications on the mother-NICUs to avoid prolonged maternal absences.

8.4.3.2.2.3 Health care worker and health system factors affecting daily duration of skin-to-skin contact

Absence of formal KMC counselling for mothers and families is the most important barrier to successful implementation of KMC for preterm neonates, including those receiving oxygen and non-invasive ventilation.[197] Formal counselling was provided at the time of eKMC trial enrolment, but this could have been strengthened especially at the time of maternal availability and “handing-over” to the mother. Use of visual aids, videos and other culturally appropriate health education materials could also have strengthened the counselling process and contributed towards improved KMC duration. We were unable to provide 1:1 nursing support for KMC providers compared to the iKMC trial which had a dedicated team focused on supporting the mothers with KMC provision.[64] This possibly contributed to the higher daily duration observed during the iKMC trial due to ongoing maternal sensitisation, education, reassurance and support.

Understanding HCW perceptions of providing KMC to unstable neonates is critical for implementation if there is a shift in global policy. Morgan et al identified HCW (n=10) acceptance of early KMC alongside other medical interventions, albeit with concerns about ensuring adequate monitoring.[153] During the early eKMC trial period (June – July 2018) a linked qualitative study was conducted to explore HCW perceptions towards the intervention. This involved 11 in-depth interviews with nurses and doctors of all cadres at the trial site, with thematic analysis using an established framework for evaluation of new health interventions.[213] Overall, there was mixed acceptability of the intervention with concerns about safety and effectiveness yet a willingness to support the intervention if shown to be effective. Barriers and concerns identified by HCW at the eKMC trial site included: 1) Maternal unavailability and financial implications for prolonged hospitalisation of mothers/families; 2) Lack of beds, space, privacy and WASH facilities to enable a comfortable environment for KMC providers within the NNU; 3) Inadequate monitoring of unstable neonates in KMC position out-with a research setting due to lack of sufficient pulse oximeters for continuous monitoring; 4) Safe provision of IV fluids whilst newborn was in the KMC wrapper with potential for obstruction or dislodgement of IV cannula and fluids. Enabling factors were identified as: maternal empowerment in caring for their newborn; reduced workload for HCW; education and sensitisation of HCW about the intervention; and maternal support from family members.[214] The factors identified in this qualitative study may have contributed to the low duration of KMC delivered, although attempts were made to mitigate these findings in real-time with enhanced HCW sensitisation and training on safe provision of early KMC, especially to avoid IV fluid administration issues.

The iKMC trial focused on treating the mother and baby as a combined unit, by establishing mother-NICUs where the mothers could stay comfortably with their newborn/s and receive all necessary medical care. Providing a conducive, comfortable and respectful environment for KMC providers is fundamental for prolonged KMC and is possible only with focused health systems adaptations and resource/financial investment. Although we attempted this during the eKMC trial (Chapter 3), it is challenging within the confines of existing ward structures and health-systems limitations. Visitation policies can also preclude prolonged KMC duration[212] and are an important barrier to mitigate in a culturally sensitive way, using participatory approaches with involvement of parents and families.

8.4.3.2.3 Limitations in measurement of duration spent in KMC position

Acknowledging the limitations in measuring KMC duration during the eKMC trial is important for interpretation of the fidelity of the intervention and for wider consideration of this as a priority topic within KMC research.

KMC measurement was directly observed by eKMC nurses using paper CRFs at the bedside. The data was manually inputted to an Excel spreadsheet and then the total daily duration data was reconciled with the electronic trial database. The main limitation with this method is potential data inaccuracies linked to the lack of a dedicated person responsible for data collection and multiple other responsibilities which research nurses had within the confines of a small team. Research nurses were responsible for all recruitment and routine research data collection, with time-pressured tasks such as screening and consenting prioritised over more routine tasks such as KMC documentation. Due to the small team and budget limitations, it was not possible to have separate, independent KMC duration assessors. Hence, there is a risk that KMC duration was under-recorded due to prioritisation

of other tasks and "missing" KMC sessions. Conversely, this may also have resulted in over-estimation with data heaping by rounding up to the nearest hour if duration was documented retrospectively at the end of a shift or "estimated". This is particularly relevant for neonates on the KMC unit, which although adjacent to the NNU, was separate from where the nurses spent most of their time and there was high risk of inaccurate recording as nurses often relied on maternal recall. Understanding how much skin-to-skin contact was provided to non-trial participants during KMC unit admission over the same period would give insights into the accuracy of eKMC duration data, but KMC duration is not routinely documented, similar to other LMIC NNUs.[67] The iKMC trial had a field assistant whose only task was to document KMC provision, hence the iKMC measurement is likely to more accurately reflect actual KMC delivered.

Other methods of KMC measurement I considered during trial set up included an app-based system for KMC providers or HCW to electronically document time spent in KMC position. I also explored the potential of neonatal wearable technology to record time spent in KMC position using a combination of temperature and position sensors to verify upright skin-to-skin position and transmit data to a tablet based application via WIFI or Bluetooth transfer.[215] At time of trial onset there were no commercially available KMC wearables which had been validated as research tools and it was out-with the scope and budget of this PhD to develop one. KMC provider methods of documentation were also considered but not pursued due to concerns about high levels of illiteracy in our population, possible large inter-observer variability and reluctance to "task-shift" onto mothers and relatives at a vulnerable time in the early postnatal period.

Accurate and reliable measurement methods for KMC duration with high internal and external validity are important for future research as well as for potential tracking of future KMC coverage targets in HMIS.[216] More detailed insights into the continuity of KMC delivered in pragmatic LMIC settings is warranted, including predictors of prolonged KMC duration and exploration of other aspects of KMC "dose" such as minimum duration and frequency of KMC sessions for intermittent KMC.

8.4.4 Effect of early kangaroo mother care on secondary outcomes & safety

8.4.4.1 Effect of early kangaroo mother care on infections

No evidence was found for between-arm differences in the prevalence of clinically suspected (RR 1.36, 95% CI 0.81 – 2.28, P=0.240) or confirmed infections (RR 1.53, 95% CI 0.65 – 3.64, P=0.333) detected between age 3d to 28d (Table 6-2). Suspected late-onset infections occurred in 15% (21/141) of control and 20% (28/138) of intervention neonates. There was 21% blood culture positivity rate across the cohort and all confirmed infections were due to gram-negative bacteria with a high prevalence of AMR. Considering the non-blinded nature of the trial, we aimed to reduce the risk of performance bias by managing both arms in the same environment to avoid confounding from different environmental exposures. We attempted to reduce the risk of detection bias with a validated clinical score for diagnosis of suspected infection[11] and to guide which participants had blood cultures taken, with a similar proportion in both arms: 21/22 (95%) of suspected infection episodes in the control arm had blood cultures versus 26/29 (90%) of suspected episodes in the intervention arm (Table 6-2). In recognition that the volume of blood is an important determinant of blood culture positivity rates,[217] we collected adequate ($\geq$1ml) and similar volumes of blood from

both groups (control arm=1.1ml (SD 0.3); intervention arm 1ml (SD 0.3); P=0.238) (Table 6-2). Laboratory personnel were blinded to allocation arm, but the field team were not, which was mitigated by use of the objective infection definitions. Caution is recommended in over interpretation of the higher observed prevalence of infections with early KMC compared to standard care due to non-significance of the finding and small sample size, indicating this is likely to be a chance finding. However, it is important to acknowledge that the trial site had known challenges in IPC before and during the eKMC trial with inconsistent running water (Chapter 3), contamination of IV fluids, antibiotics[79] and essential equipment (bCPAP, oxygen concentrators)(Chapter 3), and endemic/epidemic GNB invasive outbreaks.[79] Future mechanistic work to explore the effect of KMC on MDR-GNB carriage with paired neonate-KMC provider (mothers & other relatives) is planned.

The 2016 Cochrane meta-analysis reported 65% reduced risk of nosocomial infection at discharge or 40-41 weeks post-menstrual age (RR 0.35, 95% CI 0.22 – 0.54) and 50% reduction in severe infection at latest follow-up (RR 0.50, 95% CI 0.36 – 0.69) with KMC started after stabilisation.[48] However, this finding was based on 5 trials with only 1,239 participants for the nosocomial infection outcome and 8 trials with 1,463 participants for severe infections.[48] This is a small sample size compared with other meta-analyses exploring effects of infection prevention interventions, such as the meta-analysis of umbilical cord chlorhexidine application which included >55,000 neonates from 3 community RCTs and provided very robust evidence of effect.[218] Most of the pooled effect of the 50% reduction in severe infection reported by the 2016 Cochrane review was provided by studies with moderate or high risk of bias, due to non-blinding of outcome assessments and/or risk of performance bias (Table 8-2).[48] The analysis of KMC effect on nosocomial infections was also weighted towards the Colombian trial by Charpak et al, which was at high risk of performance and detection bias as the intervention and control arms were managed in different hospitals and outcome assessors were unblinded.[219] Boundy et al reported a similar beneficial effect of KMC on infections (RR 0.51, 95% CI 0.32 – 0.81, n=9 trials)[53] yet included the same RCTs as Conde-Agudelo et al with an additional trial conducted in Ecuador which published limited data about event rates with an overall 70% reduced risk of severe infection with KMC (RR 0.3, 95% CI 0.14 -0.67; n=283) (Table 8-2).[220]

The iKMC trial also reported evidence of a significant beneficial effect of KMC on suspected infections, although with a smaller effect size than reported by the Cochrane review at 18% relative reduction (RR 0.82, 95% CI 0.73 – 0.93).[64] However, there was also a high risk of performance bias with the iKMC infection findings, as two of the trial sites admitted control and intervention neonates to different NICUs, with newly built Mother-NICUs used for the intervention arms. The environment of a newly built neonatal unit is likely to be different from an established NICU, with possible absence of existing reservoirs of MDR-pathogens[221] and potential confounding from varying access to WASH facilities. iKMC site-specific infection prevalence data is not currently available; hence it is not possible to gain further insights into the site-specific breakdown of infections and how that may relate to context of care at each site.

Varying or absent clinical definitions of suspected infection are a feature of all RCTs included in the Cochrane [48] and Boundy systematic reviews[53] as well as the iKMC trial,[64] with no definition based on a validated score and all including non-specific signs of possible infection (Table 8-2).

Although we made efforts to use a validated clinical score to detect suspected infections during the eKMC trial, the specificity of the Rosenberg score which we used was low (50%).[11] This highlights the inadequacies in currently available clinical scoring systems to detect neonatal infections, especially for preterm neonates who may have more subtle signs. Confirming invasive infection is critical to evaluate the impact of interventions on neonatal infections. In addition to the eKMC trial, three other KMC trials have reported blood culture confirmed infections and none have shown evidence for KMC effect, albeit mostly due to small sample sizes and low event rates.[222-224] These trials are discussed below in detail, with their characteristics outlined in Table 8-2.

An RCT in a Malaysian level 3 NNU found no effect of intermittent (≥1h/d) KMC on blood-culture confirmed infections (RR 2.21 95% CI 0.21 - 23.76) but had very low infection rates (1/62 cases in control group, 2/64 cases in intervention group).[222] A trial in a North American level 3 NNU reported double the proportion of blood or CSF culture positive sepsis with standard care versus intermittent KMC, but the small sample size (control, 8/27; intervention, 5/33) resulted in a non-statistically significant effect size (RR 0.51 , 95% CI 0.19 – 1.38).[223] A small study at an Indian level 3 unit reported culture positive infections in 14% (6/44) of stable neonates receiving continuous (˜10h/d) KMC compared to 18% (8/45) of control arm (RR 0.77, 95% CI 0.29 – 2.03), with Klebsiella pneumoniae most commonly identified.[224] Criteria for obtaining blood cultures were absent from all three trial reports (Table 8-2), limiting assessment of potential detection bias due to intervention neonates undergoing more intensive assessment for infections. This is an inherent risk in a non-blinded trial which we avoided in the eKMC trial by pre-specifying criteria for obtaining cultures. It is also worth noting the different interventions studied in these trials, ranging from ≥1h/d to 10h/d of KMC contact, which may be an important factor in mechanisms of KMC in modulating exposures to and risk of infections.

A recent systematic review of interventions to reduce hospital-acquired neonatal bloodstream infections (BSI) included data only from Charpak et al and Boo et al, with other KMC trials excluded as ICROMS Quality Criteria were not met. This review found moderate evidence for KMC as an intervention to reduce BSI and called for more multisite trials with robust designs to inform IPC strategies in resource-limited NNUs.[225] The iKMC team are planning on publishing their culture-positive infection data (personal communication from iKMC team), which will give valuable data and insights. Despite the inherent limitations with heterogeneous definitions and risk of bias, future meta-analyses may be able to pool microbiologically confirmed infection outcomes and provide more insights into the IPC effects of KMC.

The eKMC trial findings for suspected and confirmed infections should be considered in the context of the environmental surveillance findings at baseline and every 6-months during eKMC trial recruitment period (Chapter 3, Annex A-4). We identified sustained presence of pathogenic GNB at the trial site for the duration of the recruitment period, including extrinsic contamination of IV fluids, sinks, and equipment (suction machines, bCPAP machines and oxygen concentrators). We cannot yet link the surveillance isolates with invasive isolates from eKMC participants nor quantify the burden of bacterial presence on the NNU, but this finding gives insights to the nosocomial context during the eKMC trial. Understanding the impact of this high risk environment on eKMC trial participants is out with the scope of this PhD but will be explored in future work with detailed genomic analysis of environmental, carriage and invasive isolates.

Table 8-2. Randomised controlled trials reporting kangaroo mother care effect on infection outcomes

RCT	Setting	N° Participants & entry criteria	Control (Standard care)	Intervention provided (KMC)	Infection as outcome	Risk of bias	Definition of infection / nosocomial sepsis	Between-arm differences in infections	Effect size[a] (95% CI)
Ali 2009[187] b, c	India Level 3 NNU	N=114 1200 - 1800g Stability not specified	Radiant warmer or open cot in warm room	Starting age 4.7d[d] Duration 6.3 h/d[d]	Yes	Unclear risk[e]	Mild-moderate infection: Oral antibiotics/no admission Severe infection: IV antibiotics/admission. Included pneumonia, diarrhoea & sepsis Nosocomial infection: No definition provided No blood cultures	Severe infection: KMC: 3/58 (5) SC: 10/56 (18)	Severe infection: RR 0.29 (0.08 – 1)
								Nosocomial infection: KMC: 4/58 (7) SC: 13/56 (23)	Nosocomial infection: RR 0.3 (0.1 – 0.86)
Boo 2007[222]b, c	Malaysia Level 3 NNU	N=128 <1501g; Stable on CPAP/oxygen	Incubators and cots	Starting age 24.5d[f] Duration1h/d[f]	No	Unclear risk[e]	Clinical criteria not fully defined ("Symptomatic infant") Blood cultures obtained	KMC: 2/56 (4) SC: 1/62 (2)	Severe infection: RR 2.21 (0.21 - 23.76)
Eka Pratiwi 2009[226]b,c	Indonesia Level 3 NNU	N=93 1500 – 2250g Stable[g]	Incubators or open cribs in warm rooms	Starting age <24h Duration 10h/d[d]	No	High risk Unblinded outcome assessors	No definition provided No blood cultures	KMC: 1/48 (2) SC: 3/45 (7)	Severe infection: RR 0.31 (0.03 – 2.9)
Kadam 2005[224]b,c	India Level 3 NNU	N=89 ≤1800g Stable in air	Radiant warmers	Duration 9.8h/d[d]	Yes	Unclear risk[e]	No definition provided Blood cultures obtained	KMC: 6/44 (14) SC: 8/45 (18)	Severe infection: RR 0.77 (0.29 – 2.03)
Kumbhojkar 2016[227]b	India Level 3 NNU	N=120 <2000g Stable, [g] on IV fluids	Radiant warmer or cradle with hot lamp	Daily duration 11.5h[d]	Yes	Unclear risk[e]	No definition provided for severe sepsis or nosocomial sepsis No blood cultures	KMC: 2/60 (3) SC: 14/60 (23)	Severe & nosocomial infection: RR 0.14 (0.03 – 0.6)
Rojas 2003[223]b, c	USA Level 3 NNU	N=60 <1501g ≤32 weeks Stable on vent/ CPAP/oxygen	Incubator	Duration 1.3h/d[d]	Yes	Unclear risk[e]	"Clinical deterioration" (not defined) AND Blood or CSF cultures obtained	KMC: 5/33 (15) SC: 8/27 (30)	Severe infection: RR 0.51 (0.19 – 1.38)
Rao 2008[181]b, c	India Level 3 NNU	N=220 <2000g Stable[g]	Radiant warmer[g] or cradle with hot lamp	Duration 13.5h/d[d]	Yes	Unclear risk[e]	No definition provided No blood cultures	KMC: 4/103 (4) SC: 15/103(15)	Severe & nosocomial infection: RR0.27 (0.09 – 0.78)

RCT	Setting	N° Participants & entry criteria	Control (Standard care)	Intervention provided (KMC)	Infection as outcome	Risk of bias	Definition of infection / nosocomial sepsis	Between-arm differences in infections	Effect size[a] (95% CI)
Charpak 1997[219]b, c	Colombia Level 3NNU (SC) and Paediatric hospital (KMC)	N=777 <2000g Stable[g]	Incubator	Data on age at starting KMC & KMC duration not reported	Yes	High risk Control & intervention arms in different hospitals	Infection=All infectious episodes needing antibiotics Severe infection=Nosocomial infections needing systemic antibiotics or detected after discharge & needing admission No blood cultures	Severe infection: KMC: 26/343 (8) SC: 35/320 (11)	Severe infection: RR 0.69 (0.43 – 1.12)
								Nosocomial infection: KMC: 13/343 (4) SC: 25/320 (8)	Nosocomial infection: RR 0.49 (0.25 – 0.93)
Ghavane 2012[180]b, c	India Level 3 NNU	N=140 <1500g; Stable (no oxygen / resp. support)	Radiant warmer or incubator	Duration >8h/d	No	Unclear risk[e]	No definition provided No blood cultures	Nosocomial infection: KMC: 2/68 (3) SC: 2/68 (3)	Nosocomial infection: RR 1 (0.15 – 6.9)
Sloan 1994[220]c	Ecuador Maternity hospital	N=283 <2000g Stable[g]	Incubator or thermal crib	Data on age at starting KMC & KMC duration not reported	Yes	Unclear risk[e]	Clinical definition based on history & examination: Diarrhoea; urinary infections; pneumonia, septicaemia, general infections No blood cultures	Raw data not known for infection outcomes. Grouped as per mild/moderate/ severe illness	Severe infection: RR 0.3 (0.14 – 0.67)
iKMC, 2021[64]	India Ghana Nigeria Malawi Tanzania Level 3 NNU	N= 3,136 1 – 1799g Stable & unstable (Able to breath on own +/- oxygen/bCPAP)	KMC started at age >24h & "when infant began to recover"	Starting age 1.3h[f] Duration 16.9h/d[f, h]	Yes	Medium risk Independent outcome assessors Different NICUs at 2 sites for SC/KMC arms	Clinical deterioration after initial improvement & age 24h with ≥1 of: Chest in-drawing; Temp <35.5°C or >38°C; Lethargy; Seizures No blood culture data available	KMC: 361/1575 (23) SC: 434/1561 (28)	RR 0.82[i] (0.73 – 0.93)
eKMC, 2021[206]	The Gambia Level 2/2+ NNU	N=279 <2000g Unstable on oxygen & IV fluids	Non-servo controlled radiant warmer or incubator	Starting age 15.2h[f] Duration 6.7h/d[f]	Yes	Low risk Unblinded assessors for suspected sepsis, blinded for confirmed sepsis A-priori criteria for obtaining cultures	Suspected late-onset infection (LOI) ≥1 of "clinical deterioration" criteria AND Age ≥72h with ≥1 of: Apnoea, pallor, lethargy, jaundice, hepatomegaly (Rosen Confirmed LOI: Meets suspected LOI criteria AND positive blood culture	Suspected LOI: KMC: 28/138 (20) SC: 21/141 (15)	RR 1.36 (0.81 – 2.28)
								Confirmed LOI: KMC: 6/138 (4) SC: 4/141 (3)	RR 1.53 (0.65– 3.64)

a) Effect size as presented in Cochrane 2016 review, except for Sloan 1994, iKMC 2021 and eKMC (Chapter 6); b) Trial included in Cochrane 2016 systematic review and meta-analysis review;[48] c) Trial included in Boundy et al systematic review and meta-analysis;[53] d) Mean values presented; e) Unclear risk of detection bias as no information provided on blinding of outcome assessors and/or criteria used to determine which neonates had blood cultures taken; f) Median values presented; g) Description of stability criteria for trial entry did not include information about level of respiratory support; h) Median duration in iKMC trial 16.9h/day whilst on mother-NICU, 20.2h/d whilst on KMC ward; i) 95% confidence interval for infection outcome was not adjusted for multiplicity and authors note it should not be used to infer definitive intervention effects.

In summary, the existing evidence base for a significant infection prevention benefit of KMC is based on heterogeneous trials with small sample sizes, high risk of performance and detection bias and lack of standardised, specific and objective infection definitions. Similar to three other trials reporting culture-confirmed infections, we did not find a significant infection prevention effect associated with KMC, although this likely reflects insufficient sample size. More robust evidence incorporating standardised infection definitions with high sensitivity and specificity and microbiological or genomic data is needed to explore the IPC effects of KMC further. A more nuanced approach to understanding the infection prevention effects of KMC is warranted, taking into consideration the context of nosocomial risk in varying resource limited NNUs.

8.4.4.2 Effect of early kangaroo mother care on breastfeeding practices & weight gain

We reported a high prevalence of exclusive breastfeeding in the control arm at discharge (98%), with no effect of early KMC (RR 1.0, 95% CI 0.96 – 1.04) (Table 6-2). Similarly, the iKMC trial did not identify improved exclusive breastfeeding at discharge (RR 1.06, 95% CI 0.73 – 1.53) or 28 postnatal days (RR 1.01, 95% CI 0.98 0 1.05) but did provide detailed insights into positive effects of KMC on breastfeeding practices during admission from a post-hoc analysis. Immediate KMC was associated with: 1) More neonates starting breastmilk feeds within 24h (RR 1.29, 95% CI 1.20 – 1.37); 2) More neonates being put to the breast before 72h (RR 1.32, 95 % CI 1.24 – 1.41); 3) First attempt at breastfeeding 25h earlier than with standard care (RR 1.50, 95% CI 1.40 – 1.62) and more neonates reaching full breastmilk feeding within 7d (RR 1.14, 95% CI 1.09 - 1.19).[64] It is worth noting that mothers were recruited to iKMC trial only if they were likely to provide the majority of KMC within the first 3 days. This differs from our eKMC cohort, in whom female relatives played a greater role in KMC provision during the first 3 days. This may have affected feeding practices, due to unavailability of mothers' milk and reduced contact for breastfeeding opportunities with female relatives as primary KMC provider. The eKMC trial definition of exclusive breastfeeding is consistent with one of the definitions used in the iKMC trial, "Only receiving breast milk and no other liquid or solid, with the exception of vitamin or mineral supplements or medicines, if prescribed"[64] but may differ from other KMC trials in which "breast-milk feeding" may be the preferred terminology. This underlines the importance of core outcome sets with aligned definitions for future trials of feeding interventions.

The eKMC trial did not demonstrate a clinical or statistically significant improvement in weight gain at 28d of age with early KMC (10.3g/d) compared to standard care (12.5g/d)(MD -2.2, 95% CI -5.28 to 0.81, p=0.150), despite being adequately powered to detect a difference (Table 6-2).[206] Sub-group analysis did not reveal any significant effect depending on admission weight category, although neonates <1200g had lower mean weight gain by approximately 6g/d in both arms compared to neonates $\geq$1200g (Table 6-3).224 Overall, there was low absolute weight gain for the eKMC cohort, with the minimum acceptable threshold of 10g/kg/day only just reached and inadequate weight gain in the sub-group of neonates with admission weight <1200g regardless of KMC provision (6.1g/day in control; 6.9 g/day in intervention. Table 6-3). This may also have precluded any detection of evidence for effect of the intervention. The iKMC trial did not include weight gain as a secondary outcome but this is an endpoint in the OMWaNA trial.[65]

There is strong evidence for the effect of KMC on weight gain in stable newborns, with neonates 4.1g heavier (95% CI 2.3 – 5.9, 11 intermittent KMC trials, n=1198) in the KMC group compared to

conventional care at latest follow-up.[48] The evidence for effect of KMC on weight gain at specific time-points such as hospital discharge or 40-41 weeks postmenstrual age (MD 16.1g, 95% CI -44 to 47; 5 trials, n=1233), 6 months (MD 78g, 95% CI -52 to 209; 1 trial, n=591) and 12 months follow up (MD 31g, 95% CI -135 to 198, 1 trial, n=596) is less convincing with wide confidence intervals crossing zero at all time-points.[48] A recent systematic review reported a moderate impact of KMC in stable neonates on growth, with high heterogeneity among studies but, interestingly, found a dose response relationship for weight gain, with infants who received at least 6h/d KMC contact gaining more weight than control or neonates receiving <2h/day (mean difference in weight 8.99g, 95% CI 8.14-9.84).[54]

Our findings suggest that early KMC in unstable neonates may not have the same effect on weight gain as starting KMC contact after stabilisation in settings with limited feeding and nutritional support. Excessive weight loss and slow weight gain in critically unwell neonates are recognised phenomenon due to multifactorial pathways,[228] with lower weight and gestation neonates at particular risk. Parenteral nutrition (PN) was not available at EFSTH, like many other African NNUs,[229] and reflects health system challenges in preparation, storage, administration and monitoring of PN. eKMC participants received only 10% dextrose plus sodium/potassium until enteral milk feeds were established. This is nutritionally sub-optimal, with lack of protein, fat, vitamins, micronutrients (e.g., zinc) and essential electrolytes such as calcium and phosphorous, all of which are needed for illness recovery as well as growth, bone health and neurodevelopment. This may have contributed to our observed low absolute weight gain within the neonatal period. Nasogastric tubes were used to support feeding in 86% (control arm) and 91% (intervention arm) of eKMC trial participants, indicating high compliance with some of the WHO's recommended quality feeding standards.[22] However, as only 54% of intervention mothers were present within the first 24h (Table 6-4), access to the preferred option of expressed breast milk was initially limited. Female relatives were encouraged to obtain expressed breastmilk from the remote mother and feed via gastric tube until mother was on-site, but the extent of this practice is not known. In the absence of mother's expressed milk, infant term formula milk was used during the admission in 17% (24/141; control) and 20% (28/138; intervention) as a temporary measure (eTable6-6). This high rate of formula usage was not reflected in the low rates of formula milk at time of discharge, underlining the need for carefully considered outcomes in future trials to reflect the complexity of preterm feeding. Considering the dose-response relationship between KMC duration and weight gain,[54] it is also possible that low fidelity of the intervention may have contributed to a lack of difference in growth.

Donor breast milk is recommended as the best alternative for feeding preterm neonates when mother's milk is not available[149, 230, 231] but there are few human milk banks operational in LMICs, especially in SSA,[232] with the exception of South Africa.[233] Perceptions of caregivers and HCW towards donor human milk banking has previously been explored in East Africa, with overall willingness of mothers towards donating and feeding children with human milk and barriers including fears of HIV transmission and poor hygiene,[232, 234] but there is a dearth of published data from West Africa.

PN is recommended by WHO if enteral feeding cannot be used for small and sick newborns,[22] but detailed guidance about how to safely provide PN in the lowest resource settings is not yet available and is an important policy gap. PN introduction in low-resource settings is complex, with barriers

including need for aseptic preparation,[235] safe storage and administration via central or peripheral lines,[236] and reliable biochemical monitoring to detect and manage adverse effects such as hyperglycaemia, and electrolyte disturbance.[236] HCW training and competence is also essential prior to PN introduction with consideration of health-facility costs.

Other aspects of nutritional management in our cohort were sub-standard as per WHO guidelines, although as data collection ceased at 28d, not all nutritional supplements may have been captured during the follow-up period. Fat soluble vitamins were received by 52% (144/277) of eKMC participants with folic acid in 57% (159/277) and iron supplementation in 10% (28/279) (eTable6-6). Vitamin D, phosphate, zinc, and calcium supplements were not available as standard care.

In summary, we did not identify an effect of early KMC on weight gain at 28-days or breastfeeding rates at discharge for unstable neonates compared to standard care. As identified in the iKMC trial, immediate KMC is associated with improved breastfeeding metrics during NNU stay. Our findings may have been influenced by a high rate of non-maternal KMC providers and the context of suboptimal feeding/nutritional support for unstable neonates. Also, exploring feeding practices at discharge does not adequately represent the complexity of feeding for neonates <2000g, nor give insights to how early KMC may impact on feeding practices alongside other SSNC interventions. More policy/programmatic focus on nutritional support of small and sick newborns in LMICs is needed, especially for neonates <1200g. Key evidence gaps include barriers and enablers to human donor milk use, scale-up of PN where feasible, and innovative trials of pragmatic and safe feeding interventions.

8.4.4.3 Effect of early kangaroo mother care on duration of stay and hospital re-admission

Our cohort were admitted for median 16-days, and we found no evidence for between-arm differences in duration of stay (MD +0.3d, 95% CI -60.5 – 75.1) (Table 6-2). This is similar to the mean duration of stay reported from the iKMC trial (15.2d, control versus 14.9d, intervention), with no effect size also detected in this larger cohort.[64]

Duration of admission in the eKMC trial was determined by pre-specified criteria based predominantly on the need for clinical stability, adequate weight gain and absence of need for supplemental feeding via gastric tube. Neonates with admission weight <1200g had more than twice the duration of admission compared to neonates ≥1200g (mean 29.4d versus 13.3d respectively in control arm; mean 28.2d versus 14.5d respectively in intervention arm, Table 6-3). Contrary to what we expected, the sub-group of neonates born from a twin pregnancy had shorter hospital admissions compared to singletons by approximately 3 days and no between-arm difference was observed for duration of stay for either twins or singletons (Table 6-3). There is evidence from the Cochrane 2016 review that intermittent KMC (started after stabilisation) reduces duration of hospital stay by 1.6d (95% CI -3.4 – 0.18).[48] However this is derived from 11 RCTs of small size each (total n=1057) with high heterogeneity. Boundy et al also reported no evidence for effect of KMC on reducing duration of stay from analysis of 12 trials, although they highlighted one trial with a sub-group finding of shorter admission with KMC for neonates <1500g.[53]

Rates of re-hospitalisation within postnatal 28d were no different between treatment groups, with 4% (5/141) of control arm and 3% (4/138) of intervention arm re-admitted (eTable6-4). Only two

other RCTs reported re-admission data with no statistically significant effect of KMC previously observed. As we had low loss to follow up rates, we are confident that we did not miss re-admissions or out of hospital deaths. This is reassuring considering that the minimum discharge weight was 1.1kg and previous studies have reported discharge weight <1500g as being associated with outpatient mortality.[237] This finding supports the principle of early hospital discharge with continuation of KMC in the community and close follow-up as a safe strategy, even for VLBW, to enable early discharge and reduce inpatient congestion and HAI risk.

In summary, the eKMC findings are consistent with other evidence that early KMC does not reduce duration of hospital stay. Considering the results of all high quality KMC RCTs, including different timing of onset and stability levels, the evidence that KMC reduces admission duration or prevents re-hospitalisation is not convincing. The OMWaNA trial will also provide important data for this outcome.[66]

8.4.4.4 Safety of early kangaroo mother care prior to stability

We observed that clinical deterioration in unstable neonates <2000g receiving KMC occurs frequently, with one-third of eKMC intervention arm participants switching to standard care due to becoming severely unstable, requiring resuscitation, bCPAP or phototherapy (Table 6-4). All events were deemed unrelated to the intervention and this likely reflects the vulnerable nature of small and sick newborns. Kadam et al reported a similar rate of KMC "stopping" during a pilot RCT of KMC in India, in which 34% of stable neonates were transferred to standard care for clinical reasons.[224] No iKMC trial data is available for insights into their need to stop KMC due to clinical deterioration, but as they concomitantly provided bCPAP/ventilation and KMC as part of the intervention, it is possible that they did not cease KMC for clinical reasons. None of the events occurring during early KMC were directly attributed to the intervention and we did not identify any association between early KMC and increased risk of hyperthermia, glycaemic dysregulation or abnormal vital signs (Chapter 7). In addition, 48% (22/46) of eKMC trial participants who reverted to standard care later met clinical criteria to re-start KMC. The iKMC trial does not explicitly comment on safety of immediate KMC before stabilisation, but their findings are consistent with a positive safety profile, namely no increase in hypoglycaemia, reduced risk of death and no increase in sudden death.

Evidence from HIC suggests that KMC alongside invasive and non-invasive respiratory support is not associated with adverse peripheral oxygen saturation, heart rate or cerebral oxygenation.[238, 239] There is less data available from LMIC settings, although a study of 20 LBW neonates (mean birth weight 1390g +/-484g) managed on an Indian tertiary NICU reported no differences in respiratory rate and oxygen saturations but marginal increases in heart rate and fraction of inspired oxygen (FiO_2) during 1 hour sessions of KMC with no airway extubation or IV cannula dislodgement.[240]

In summary, based on our findings and supported by other evidence, early KMC in unstable neonates receiving oxygen can be considered safe when continuous pulse oximetry and close clinical scrutiny are provided. Pragmatic efficacy studies measuring other stability indicators such as cerebral oxygenation and end tissue perfusion should be undertaken in varied LMIC settings to explore the safety profile further. However, understanding the risks in pragmatic, non-research settings is important prior to changing global policy and practice, as the context of care is likely to differ with less safety oversight. This should be linked to understanding the perceptions and attitudes of health

workers, parents, and families towards the safety of early KMC to identify and mitigate potential safety issues and implementation barriers.

8.4.5 Summary of discussion for objective 2

The eKMC trial primary outcome finding does not support recommending changes to international policy for earlier initiation of KMC onset in unstable neonates. The lack of evidence for mortality effect was likely due to a combination of low power to detect a difference and low fidelity of the intervention. The iKMC trial provides evidence for 25% mortality effect with immediate KMC provided at level 3 NNUs, especially in India, and additional data from level 2/2+ NNUs including stratification by stability status, is needed. Our infection outcome findings are methodologically robust but lack power for definitive conclusions and there is a need for more research into the IPC effects of KMC with well-designed mechanistic and effectiveness studies. Effects of early KMC on weight gain, breastfeeding and duration of admission were not observed, and underline the complexity of preterm feeding, including importance of maternal availability for optimal KMC nutrition and provision of other recommended nutritional support. KMC alongside oxygen or CPAP therapy is likely to be safe with appropriate monitoring but safety insights from pragmatic settings and stakeholder perceptions should be considered further. Detailed qualitative studies are required to understand perceptions and lived experiences of providing early and prolonged KMC to unstable neonates in a range of settings and including the voices of key stakeholders such as parents, female family members, HCW and the wider community. This is a programmatic priority if the global KMC policy shifts towards recommending immediate or early KMC initiation and is critical to promoting safe and effective KMC.

8.5. Objective 3: Pathways to mortality and effect of early kangaroo mother care on physiological factors (Chapter 7)

8.5.1 Findings from exploratory mechanisms analyses

Exploratory analyses identified important mortality reductions temporally associated with the eKMC trial. These mortality reductions were possibly influenced by implementation of recommended SSNC and eKMC trial implementation and have been described in detail in section 8.4.3.1.1, hence will not be discussed again here. An original framework was developed to conceptualise mechanisms by which early KMC may influence physiological and care pathways leading to preterm mortality. This focused on six inter-linked pathways: thermal control; cardio-respiratory stability; stress response; gastro-intestinal stability; infections and monitoring. Three key factors were associated with mortality in the eKMC trial cohort on multivariate analysis: admission weight <1200g; hypothermia at baseline and hypoxaemia. Infections likely played a prominent role in the aetiology of mortality in our trial cohort but lack of detailed cause of death attribution data limits precise understanding. Detailed analyses of physiological variables during the first 24h of eKMC trial enrolment identified very high prevalence of hypothermia and hyperoxaemia, highlighting the potential for further quality of care improvements to SSNC at the site. No positive or negative effects of KMC on thermal control, glycaemic regulation or cardiorespiratory stability were identified but there were important limitations to the design of this post-hoc analysis which limit interpretation.

8.5.2 Pathways to mortality for neonates <2000g in relation to existing literature

Our findings underline the complexity of pathways to mortality in neonates <2000g, especially for preterm neonates, with multiple interlinked co-morbidities and contributory factors.

8.5.2.1 Factors associated with preterm mortality

Admission weight <1200g, hypothermia and hypoxaemia during early neonatal admission are associated with increased risk of neonatal mortality. This reflects what is already known from a range of settings and highlights the vulnerability of the smallest and most immature neonates. Further delineation and categorisation of very-low birth weight (<1kg) populations is important as reliance on weight alone gives limited insights to clinical prognosis. Neonates weighing <1200g comprise of a heterogeneous mix of phenotypes depending on gestational age, weight for gestational age and prenatal exposures. For example, a 1000g newborn born at 35 weeks who is severely growth restricted due to maternal pre-eclampsia will have a different prognosis and pathway to survival (or mortality) compared to a 1000g newborn born at 29 weeks with appropriate growth and idiopathic preterm delivery. More standard definitions of vulnerable phenotypes would enable targeted evaluation of interventions and more precise global estimates of preterm and LBW birth and mortality rates.

The importance of hypothermia and thermal control in improving outcomes is also well recognised and our findings support the need for enhanced focus on high quality thermal control in SSNC policy and programmes. The association between hypoxaemia and neonatal mortality may reflect more severe conditions at baseline, such as RDS, and underlines the need for optimal respiratory support as an essential component of SSNC with or without KMC, with huge potential for saving newborn lives.

8.5.2.2 Need for improved cause of death attribution

Understanding the causes of death of eKMC participants was limited by lack of supportive information from verbal autopsy, post-mortem examination, or supportive investigations (e.g., Blood cultures at <72h of age and chest or abdominal X-rays). Existing verbal autopsy tools have reasonably good sensitivity and specificity for diagnosing death due to “complications of prematurity” when tested in high neonatal mortality South Asian settings,[241, 242] but lack the granularity needed to determine the precise aetiology, assess contribution of factors such as hypothermia and to reflect the complexity of preterm mortality pathways. Improved tools which incorporate vulnerable phenotypes (preterm, LBW, SGA) and are linked to post-mortem (especially infection) biodata are needed to improve national and global cause of death attribution data.

8.5.2.3 Importance of infections and AMR in pathways to mortality

Infections play an important role in the pathways to preterm mortality, as shown by the eKMC trial (Chapter 7) and iKMC trial[64] which both assigned suspected or confirmed infection as the most common primary cause of death. This is consistent with findings from longitudinal studies such as the initial findings from the CHAMPS mortality surveillance network[85] and is slightly higher than that reported by the SIP study which focused exclusively on causes of death in premature neonates in Ethiopia.[86]

The CHAMPS longitudinal surveillance study was established in 7 high neonatal mortality burden settings (Kenya, Ethiopia, Sierra Leone, Mali, Mozambique, South Africa, and Bangladesh) in 2016 and conducted detailed post-mortem examinations to investigate childhood and neonatal cause of death. Along with standard bacteriology culture of blood and CSF, malaria rapid detection tests and thick/think blood films and HIV PCR, TaqMan Array (PCR) Cards were used to detect nucleic acid material for 116 pathogen (bacterial, viral, fungal) targets from lung tissue, blood, CSF, rectal brushings, and naso-pharyngeal swabs. Overall, 53% (240/449) of neonatal deaths involved at least one infectious agent in the causal chain to mortality, most commonly Acinetobacter baumannii (40% of infectious cases), K pneumoniae (31%) and E coli (11%). For deaths of preterm neonates, 62% (141/227) had an infectious agent identified which was considered by an international expert panel to have contributed to their death, although causality was not determined, with potential for pathogen carriage as opposed to invasive infection.[85] The SIP study conducted longitudinal follow-up with nearly 5,000 preterm Ethiopian neonates and assigned cause of death by multidisciplinary expert review of clinical, laboratory (WBC, CRP, blood culture), MITS and autopsy data, using ICD-10 to categorise death causation. The cohort consisted of predominantly moderate to late preterm neonates (78.5%) with the majority weighing ≥1500g and complete autopsy data available in 40% of preterm deaths. Neonatal infections (combined sepsis, pneumonia, and meningitis) accounted for 29.8% (331/1109) of preterm deaths, second only to RDS as the main primary cause of death.[86]

Approximately one in five hospitalised neonates <2000g enrolled to the eKMC trial developed suspected or confirmed late-onset infections with aetiology due to GNB in all confirmed cases and high resistance to gentamicin and third generation cephalosporins. This is consistent with other studies showing that GNB, especially *Escherichia coli* and *Klebsiella pneumoniae,* are the most common bacterial pathogens causing neonatal infections in African hospital settings. with resistance to beta-lactams in 68% and aminoglycosides in 27%.[107] Recent data from the NeoAMR research network, collected from 39 NNUs across 12 LMIC countries, reported that 26 – 84% of GNB invasive isolates were resistant to at least one third-generation cephalosporin with 72% (26/36) in Nigeria.[108] The eKMC finding of 82% beta-lactam and aminoglycoside resistance is higher than reported in the NeoAMR network. Of additional concern is the increasing global reports of carbapenem resistant GNB, with GNB isolates from Bangladesh exhibiting 81% (47/58) resistance, although West African rates were lower at 19% (26/36).[108] We were unable to report on carbapenemase resistance from our eKMC cohort as this was not part of routine antibiotic susceptibility testing protocols at MRCG Clinical Laboratories. However, meropenem use was low in eKMC participants treated for suspected late onset sepsis (4/49, 8%, eTable 6-6) and was reserved as third-line cover for the most critically unwell neonates if available from sporadic external donations. This finding of a very high invasive AMR rate with limited sensitivity to WHO recommended antibiotic regimes highlights the urgent need for active neonatal AMR surveillance, linked to antimicrobial stewardship and improved access to effective antimicrobials.

8.5.2.4 Understanding routes of preterm acquisition of AMR pathogens and HAI

Understanding how neonates <2000g acquire AMR carriage and HAI on LMIC NNUs is also critical for designing and evaluating IPC interventions, including KMC. A detailed transmission modelling study conducted on a level 2 NNU in Madagascar with high rates of neonatal and maternal phenotypic extended spectrum beta lactamase producing gram-negative bacteria (ESBL-GNB) carriage, reported that the transmission sources for newborn ESBL-GNB colonisation are species dependent.[243] ESBL-

E coli acquisition was linked to indirect environmental contamination and ESBL-K pneumoniae to contact with colonised health care workers.[243] Family members, including mothers, were not implicated in neonatal ESBL-GNB transmission in this setting, despite high rates of maternal ESBL-GNB stool carriage.[243] Conducting similar research in varied African NNU settings, with inclusion of environmental, HCW, family and neonatal samples and linkage to genotypic MDR data is needed to understand and mitigate infection risk for neonates <2000g through more precise targeting of IPC interventions.

8.5.3 Summary of discussion for objective 3

We used process data to quantify the direct mortality benefits associated with clinical trial participation and the substantial gains possible via implementation of recommended SSNC. This enabled understanding of why we did not show a mortality effect during the eKMC trial and adds to the literature for the positive benefits for trial participants in high-mortality burden settings. Improved cause of death attribution data is required at local, national, and global level with linkage to specific vulnerable phenotypes. Improved compliance with international recommendations for thermal, glucose and pulse oximetry monitoring are needed, with linked health worker training and improved monitoring devices. Addressing these deficiencies requires a health-systems approach with changes to staffing policies, procurement, financing, and governance. Improved diagnostics and clinical algorithms for detecting infections in hospitalised preterm neonates is also a priority to enable better understanding of the contribution of infections and AMR towards mortality in this vulnerable group and to enable targeted interventions to prevent acquisition and infection with MDR-GNB.

The proposed framework for understanding pathways to mortality could help to guide process and outcome indicators and future research into mortality of neonates <2000g and the effect of early KMC. Our limited consideration of selected physiological variables could be expanded to account for the complexity of physiological responses and further research is required to understand the effect of KMC on more clinically informative indicators of stability such as end-tissue perfusion or oxygenation

8.6. Reflections on eKMC trial design, recruitment and ethics

8.6.1 Critical appraisal of eKMC trial intention & design

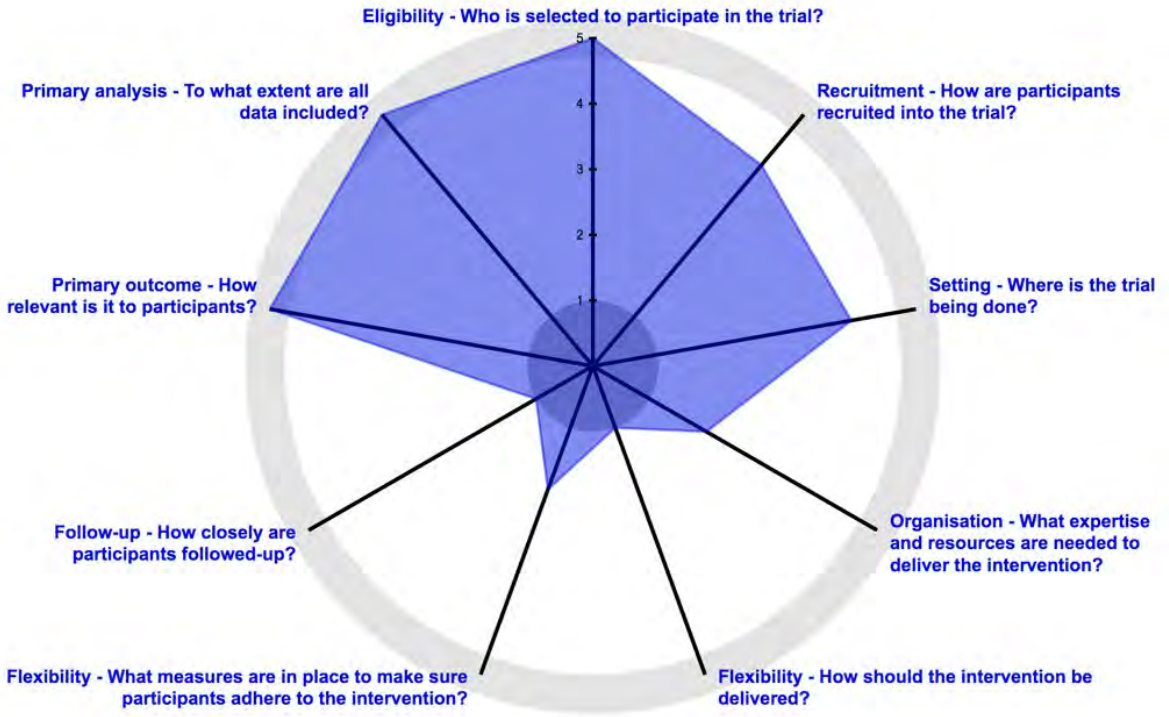
The eKMC trial was intended to be a pragmatic clinical trial to yield results generalisable to level 2/2+ NNUs in LMICs, especially in SSA (Chapter 5 & 6). The intention and design of a trial should be aligned if the trial is to yield applicable results.[244] However, there is a continuum from purely pragmatic designs in which evidence for alternative interventions is generated in usual care settings, to explanatory designs when hypotheses are tested about the interventions' mechanisms of action under laboratory-like conditions.[245] There is no simple threshold for determining where a particular trial lies on the spectrum[246] and I used the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2) instrument to define (Table 8-3) and quantify the pragmatic/explanatory nature of the eKMC trial design (Fig. 8-1).[246]

Table 8-3. eKMC trial design, as per the PRECIS-2 tool to assess pragmatic design features

Domain	Definition of pragmatic design (score 5) as per PRECIS-2 tool	eKMC trial PRECIS-2 score & explanation
Eligibility criteria	Include anyone in the trial with the condition of interest who is likely to be a candidate for the intervention if it was provided as usual care	5: ELBW neonates and twins included, to represent highest risk populations. Exclusion criteria included conditions which would preclude early KMC in post-trial setting (e.g., no study bed)
Recruitment	Recruitment takes place within a usual care setting without any overt recruitment effort	4: Recruitment was within usual context of care (i.e., all admitted neonates) but intensive recruitment efforts were made
Setting	The trial is conducted in an identical setting to which the results are intended to be applied	4: The setting is typical of level 2 newborn units in SSA, but was a single-centre trial with possibility of having unique features
Organisation	The intervention would slot into the usual organisation of care and not require any additional training, staffing or resources	2: Additional resources, infra-structure changes and re-organisation of patient flow were needed for provision of early KMC to unstable neonates
Flexibility (delivery)	The details of how to deliver the intervention would not be prescriptively described in the protocol, with flexibility for implementation in the post-trial setting. The delivery of standard care would not be prescribed in the protocol.	1: The delivery of early KMC was clearly described in the protocol with limited flexibility in how it was delivered, including criteria for temporary discontinuation The delivery of standard care was provided via a protocolised approach, with daily compliance monitoring by clinicians.
Flexibility (adherence)	Full flexibility in how end user recipients engage with the intervention.	2: Duration of time spent in KMC was proactively monitored for both control and intervention arms, linked to measures to encourage KMC duration (sensitisation of caregivers).
Follow-up	Have no more follow-up than would be the case for standard care with minimal additional data collection	1: Intensive follow-up during admission with extra clinical measurements compared to usual care, including unscheduled visits post discharge and substantial efforts to contact participants at final study visit
Relevance of primary outcome	The primary outcome is of obvious importance to participants, their families, healthcare professionals and policy makers	5: All-cause mortality is an important outcome for all stakeholders.
Primary analysis	Make no special allowance in the analysis for non-adherence or practice variability	5: The primary analysis used the intention to treat approach, with sensitivity analyses excluding ineligible participants

Abbreviations: ELBW = Extremely low birthweight; KMC = Kangaroo mother care; SSA = Sub-Saharan Africa.

Figure 8-1. Visual representation of the pragmatic/explanatory nature of the eKMC trial design, as per PRECIS-2 tool



Source. Generated using PRECIS-2 tool.[246] Reproduced with permission.
5=most pragmatic; 1=least pragmatic

The most pragmatic aspects of the eKMC design were those concerning the participant population, setting, and primary outcome (Figure 8-1). The setting and population were deliberately representative of WHO level-2/2+ hospital care for small and sick newborns, typical of district and regional hospitals in many SSA countries. Extremely low birth weight (<1kg) newborns were included to understand the intervention effect in those with the greatest mortality risk and, thus, greatest potential benefit. Likewise, including twins was intended to reflect the West African neonatal population, which has a high twinning rate,[247] and to generate pragmatic insights into providing early KMC to unstable twin pairs.

The more explanatory domains were those in which a proscriptive approach was needed due to either the unblinded nature of the intervention or to ensure safety monitoring and satisfy international ethical requirements.[1] For example, the implementation of a standardised guideline with daily compliance monitoring resulted in low risk of performance bias with similar concomitant medication and respiratory support use but provided less flexibility in delivering standard care. Likewise, criteria for when to stop and re-start KMC were included in the protocol for safety reasons, yet resulted in a more controlled, less pragmatic delivery of the intervention. The follow-up of participants during hospital stay and after discharge was more intense than the standard care at the site, with a high volume of additional data collected and close oversight of participants. Although this was balanced between arms, it reduced the pragmatic design, as well as possibly contributing towards improving the quality of care for trial participants and impacting on mortality reduction with effect on statistical power. An aspect of the research which is not captured by the PRECIS-2 tool is the preparation work conducted at the trial site (Chapter 3) prior to trial onset, which substantially

changed the reality of SSNC and reduced the pragmatic nature of the research, as previously discussed in this thesis. An example is the environmental surveillance activities, which were intended to monitor changes to background IPC exposures, but potentially resulted in improved IPC through detection and mitigation of nosocomial risk. This would have affected both arms similarly, unless there were inherent differences in the behaviour of participants or their families, e.g., intervention arm mothers having more direct contact with their newborn or reduced duration of time receiving IV fluids in the intervention arm.

The challenges in balancing a pragmatic trial design with the need to adhere to international regulatory and ethical standards are well recognised.[248] This is accentuated during a non-blinded trial, such as eKMC, where the need to reduce selection and performance bias on an individual level is essential for internal validity of the results. The need for close safety monitoring of a new intervention is also a regulatory and ethical requirement[1] and, during the eKMC trial, this necessitated closer clinical scrutiny than was usually provided. Alternative pragmatic trial designs, such as the cluster randomised trial (CRT), also have value in generating effectiveness data for complex interventions such as early KMC.[50, 249] Randomisation at the health facility level and utilisation of routinely collected health outcome data with innovative analytical methods, would avoid some of the limitations of a non-blinded individual RCT, including potential contamination of the control group. A stepped wedge CRT design could also provide an opportunity to examine how the impact of the intervention develops over time once introduced into a cluster and allow investigation of the heterogeneity in treatment effects between clusters by comparing intra-cluster outcomes during the control and intervention periods.[249] However, such trial designs may also introduce performance bias due to introduction of changes associated with intervention implementation and would require a much larger sample size to allow for cluster randomisation and correlations between individuals within the same cluster.

8.6.2 Recruitment to the eKMC trial

Recruitment barriers were identified during the eKMC feasibility study with efforts to mitigate for them in the trial protocol, including taking consent from non-parents and including female relatives in the recruitment and intervention procedures (Chapter 4). Despite these efforts, recruitment was still challenging, with only 25% of screened neonates recruited and two-thirds of the target sample size achieved.

The most frequently observed reason for non-recruitment was severe instability or death before or during the screening process (217/1107, 19.6%). This reflects the vulnerability of neonates <2000g, especially during the initial neonatal unit admission period when stabilisation may be required following transfer from the maternity unit or external health facility. Absence of a willing caregiver within the initial 24h of neonatal admission was the second most common reason for non-recruitment (168/1107, 15.2%). Despite substantial efforts to include female relatives in the screening and recruitment processes, barriers still existed due to absence of female relatives or unavailability due to her responsibility to also care for the unwell mother. The geographical separation of the EFSTH maternity wards and NNU may have also contributed to these recruitment challenges and ensuring close proximity between obstetric and neonatal services is recommended if new hospitals and mother-intensive care units are being planned.

Parents and families were unfamiliar with KMC, due to this being a relatively new practice in The Gambia. This may have also contributed to low engagement with the trial. The field team conducted sporadic sensitisation activities at EFSTH antenatal clinics from trial onset, but due to high workload with recruitment and study procedures this was insufficient to meet the recruitment needs of the trial. During year two of the trial a dedicated field worker conducted daily sensitisation activities with pregnant women and health care workers at the major referral site antenatal clinics to promote awareness of the research and encourage rapid referral and participation. On reflection, the trial would have benefited from this more intensive community engagement during the preparation phase, with inclusion of patient & health facility representatives on the trial technical steering committee to promote meaningful community participation.[250]

Availability of beds for the KMC provider was identified as an important recruitment barrier during the early trial period (May-June 2018) when recruitment rates were very low. Efforts were then made to increase the number of beds (Chapter 3). However, this required approval from the hospital management and co-ordination of the reconfiguration works without disturbing usual ward activity and was completed 8 months into the trial. Pre-trial simulations using mathematical modelling could have enabled a better understanding of recruitment challenges under different scenarios (e.g., number of beds, average duration of stay etc), utilising eKMC feasibility study data and anticipating potential risks.[251] This could have aided the operational planning of the trial with improved use of resources, resulting in a smarter, more efficient trial.[251]

8.6.3 Ethical considerations

Researchers conducting clinical trials have an ethical duty to ensure respect for participants, provide appropriate safety oversight and an acceptable risk-benefit profile, in compliance with accepted international standards for conducting research with human participants.[1] As the eKMC trial involved recruitment of unstable neonates and provision of a time-critical intervention, it can be viewed through the lens of “Emergency care research”, which has additional specific ethical considerations related to timely participant recruitment and consenting, risk-benefit assessment of standard care/intervention provision and blurring of roles between clinician and researcher.[252]

8.6.3.1 Consenting

Obtaining consent for a time-critical or emergency care trial may require a flexible consenting procedure, such as adapted or deferred consenting,[253] opt-out approaches or waiver of consent.[254] During the eKMC trial we required informed consent not only for neonatal participation and data collection, but also for family members to be willing to provide early KMC. Hence, deferred consenting was not appropriate for our needs, and we used surrogate consenting with the initial consent provided by a relative or parent followed by later parental assent/consent to continue in the trial. Obtaining surrogate consent was accepted by the local ethics committee in The Gambia with a favourable precedent that consent from non-parental family members is standard practice for neonatal and paediatric trials in The Gambia.[255] It is worth noting that no parents declined consent once initial consent had been provided and the caregiver providing consent often consulted with other family members, especially fathers and elder female relatives, via telephone during the consenting process.

Ensuring consent is truly informed for participants in emergency research is challenging, especially in the period immediately following delivery and NNU admission which is a time of high stress for parents and families[256] and requires research personnel sensitivity and empathy. Seeking consent from participants or families with a low socio-economic background also poses challenges, due to low literacy levels,[255] language barriers or relating to disempowerment due to structural inequalities, strict medical hierarchies, or other societal factors. We observed low literacy levels in our population of mothers and female relatives and ensured impartial witnesses (EFSTH junior doctors' resident in the hospital) were present to verify accurate information was provided to safeguard the participant/families' rights. Whilst this system ensured an independent, educated witness was always available and recruitment delays were minimised, there may have been unintended consequences for the quality of informed consent due to re-enforcing of power imbalances associated with having a doctor present during the consent process.

A recent mixed-methods study examined the informed consent procedures during the HELIX (Hypothermia for Encephalopathy) trial in India, Sri Lanka and Bangladesh and has provided valuable insights into the ethical issues associated with recruitment to time-critical neonatal intervention trials in LMICs.[256] Parental consent was sought within 6h after delivery and, despite compliance with ICH-GCP guidelines and quality assurance audits, the consent process was found to be largely ceremonial with limited parental understanding of randomisation and other clinical trial concepts. Parents experienced distress during the consent procedure due to their newborns critical condition, placed great trust in doctors as authority figures and were also influenced by financial implications of receiving free hospital treatments. Of concern is the finding of therapeutic misconception, where-in researchers were biased towards the intervention due to the effectiveness of cooling in HIC settings and misrepresented the intervention to parents as being an already accepted treatment.[256] There are parallels between the HELIX trial and eKMC trial consenting procedures, as we also identified high levels of respect for medical authority in our qualitative study with female relatives of hospitalised neonates (Chapter 4), which may have influenced the low consent refusal rates (<3%) and risks power imbalances during the consenting procedure. MRCG is a very well-respected institution in The Gambia and social desirability bias may also have played a role in the consenting decisions of families. Similar to the HELIX trial, the eKMC trial was non-blinded and KMC is already an established proven intervention for stable newborns. Hence, we cannot exclude the possibility that therapeutic misconception also took place during eKMC trial consenting procedures.

Obtaining prenatal consent from pregnant women is an alternative approach used in trials needing rapid perinatal or postnatal intervention delivery.[257] This approach enables women and families to consider the information without the time or emotional pressures associated with having an unwell newborn. This consenting approach was also used during the iKMC trial, with pre-screening and consenting of women at high risk of delivering an LBW baby followed by confirmation of consenting after neonatal eligibility screening.[64] Whilst this would have been a preferred approach, pre-screening and consenting thousands of pregnant women was not feasible within the budget and timelines of this PhD. Other Gambian trials have used culturally appropriate audio-visual consenting tools to aid participant comprehension during consent,[258] and this could have also been considered.

Trials in HIC countries are moving towards obtaining deferred consent for emergency care paediatric research with time-critical interventions.[259] Whether that is appropriate for neonatal clinical trials in LMICs warrants careful consideration but has previously been used in high impact trials such as the FEAST trial[253] where it was found to be acceptable to parents, health workers and researchers.[260] Innovative approaches to seeking consent, ensuring high quality informed consent with minimisation of power imbalances and providing culturally appropriate consenting tools are required for future emergency care LMIC neonatal trials.

8.6.3.2 Researcher and clinician roles

Blurring of the role between researcher and clinician is an ethical challenge during conduct of emergency care research in LMICs when clinicians responsible for providing care may have a conflict with research duties and responsibilities.[252] It is generally recommended to have separate clinical and research teams to avoid such a conflict, but this poses challenges in trials involving unwell patients conducted in settings with health systems limitations. An example during the eKMC trial was the dual role of the eKMC doctors and me as both researchers and clinicians contributing towards general neonatal care at EFSTH and oversight of the KMC unit. This was required to establish a good relationship with EFSTH nursing and medical teams, facilitate trial implementation and to enable the protocolised approach to care to avoid bias. However, inadvertent effects may have been to exacerbate differences between recruited and non-recruited neonatal care or provide a level of scrutiny to eKMC participants which would not otherwise be available and, thus, reduce the pragmatic design of the trial.

8.6.4 Summary of reflections on eKMC trial design, recruitment, and ethics

In summary, conducting neonatal intervention trials in LMICs which are simultaneously pragmatic, non-blinded and time-critical is possible but challenging and raises specific operational and ethical issues especially around recruitment, consenting and provision of standard care. I recommend using existing planning tools to anticipate and mitigate design and operational barriers, such as PRECIS-2, as well as feasibility studies and planning tools to inform context specific preparation. Innovative approaches to obtaining consent are required for neonatal emergency-care trials with time-critical interventions in LMICs, with focus on empowering meaningful and informed family participation.

8.7. Strengths and limitations of the PhD

8.7.1 Strengths of PhD

An important strength of this PhD is the science in terms of generation of original, high-quality data to give insights into SSNC, KMC as standard care and a robust RCT for early KMC prior to stability in a West African resource limited context.

8.7.1.1 Strengths of PhD objective 1: Preparation of study site and mitigation of barriers

This PhD has leveraged sustainable improvements to quality of care for small and sick newborns at the national neonatal referral hospital in The Gambia, with consideration of family-centred care at the core. These changes are temporally linked to reduced in-patient mortality rates, with participation in the eKMC trial associated with 29% relative risk reduction in 28-day mortality, directly benefiting participants, their families, and the wider community/society. Continuous KMC for stable neonates is now embedded into standard care at the major neonatal referral hospital in The

Gambia, with family-centred care an integral part of SSNC at the study site. PhD activities also contributed to promoting KMC and care of preterm newborns onto the national health agenda in The Gambia. GGMoH and UNICEF The Gambia are currently rolling out KMC at national level, with trainers and training materials developed during the KMC implementation phase central to that activity.

Novel qualitative data were generated about the perceptions of female relatives towards SSNC and KMC, adding rich insights to existing literature on caregiver's perceptions of newborn care from a West African perspective and advocating for their inclusion in SSNC and KMC programmes as essential KMC stakeholders. We used SCOPUS guidelines (SRQR) for the reporting of results, taking care to reflect on the trustworthiness and reliability of our data and incorporated an explicit framework by which to understand KMC implementation according to layers of stakeholders.

8.7.1.2 Strengths of PhD objective 2: Investigating effect of early KMC on mortality and clinical outcomes

The eKMC trial design was based on locally derived feasibility data with identification of recruitment barriers and mitigation through culturally appropriate methods. We conducted a robust individually randomised controlled trial with good adherence to international standards for quality and ethical compliance for clinical research in resource-limited settings. The efforts we made to minimise screening and performance bias were appropriate within the confines of the trial design and helped to generate high quality data for inclusion in meta-analyses, as well as providing important insights to the safety and implementation of early KMC in a resource limited NNU. We generated robust data regarding effect of KMC on weight gain and duration of stay, adding to the evidence base.

Although a rigorous process evaluation and theory of change process was out with the scope of this PhD, I developed a conceptual framework (Chapter 3) to guide collection of process and implementation data with the aim of understanding (1) How changes to standard care may have impacted on trial outcomes and (2) How to implement and deliver early KMC for unstable neonates, including perceptions of HCW, which is a critical factor. Further evaluation of this data is a next step and will help to further understand barriers and enablers for KMC in unstable neonates, in light of the iKMC trial findings.

8.7.1.3 Strengths of PhD objective 3: Exploration of pathways to mortality and effect of early KMC on physiological factors

An original conceptual framework for mechanisms of effect of early KMC in unstable neonates was developed through considering the pathways to mortality for neonates <2000g and existing evidence for KMC. The predictors of mortality we identified add to the evidence base for understanding mortality pathways for small and sick newborns. The trial platform also enabled collection of paired neonatal-mother and caregiver carriage samples (rectal, skin, and rectovaginal), which will be utilised to investigate acquisition of AMR carriage and microbiome development in hospitalised neonates <2000g with exploration of KMC infection mechanisms beyond this PhD (funding dependent). The quantification of the "healthy effect" of clinical trial participation in high mortality burden settings has value for other pragmatic trials, to ensure adequate sample size calculations and to underline the direct patient benefits of participating in clinical research.

8.7.1.4 Other strengths of the PhD

The eKMC trial platform enabled ancillary studies which maximised the value of the trial dataset without compromising PhD or trial objectives. Full description is out-with the scope of this thesis but included using eKMC trial screening data to validate a mortality risk score for neonates ≤2000g (NMR2000 score),[66] and collection of prospective biological samples linked to clinical and microbiological metadata for development and piloting of novel metagenomic approaches to detect infection and AMR (Gates Grand challenges funded, work in progress). Future sharing and re-use of eKMC trial data for pooled analyses will also add value to the financial and logistical efforts involved in trial set-up and conduct, with avoidance of research wastage.[251]

8.7.2 Limitations of PhD

Limitations of the individual studies have been discussed at length in the relevant chapters and will only be briefly mentioned here in relation to the overall PhD.

8.7.2.1 Limitations of PhD objective 1 (Chapters 3 & 4)

The study of female relatives' perceptions of SSNC and KMC was conducted prior to KMC implementation and did not include the lived experiences of women providing KMC, which limits the external validity of the findings. Although an explicit framework was used during analysis, the interpretation of the data would have benefited from consideration of a framework designed to evaluate perceptions of a new health intervention, such as the Atun framework which has been used in previous systematic reviews of this topic,[213] and would have provided consistency with the existing literature. The acceptability of providing early KMC to unstable neonates was also not explored from maternal or family perspectives which is an important evidence gap.

8.7.2.2 Limitations of PhD objective 2 (Chapters 5 & 6)

Regarding the eKMC trial, the small sample size limited the ability of the research to answer the priority question of whether early KMC in unstable neonates has mortality effect and is safe compared to standard care. We anticipated a modest (15%) reduction in baseline mortality associated with trial implementation and accounted for this in the sample size calculation but did not anticipate the extent of mortality reduction due to clinical trial participation (29%) and impact of other improvements to SSNC coverage. The baseline mortality rate was also possibly over estimated due to limitations with the feasibility study. Scenario based modelling using locally derived feasibility study data may have avoided this and provided more realistic mortality rates upon which to make sample size calculations and assess the feasibility of meeting recruitment targets.

We were not able to conduct gestational age specific sub-group analyses for eKMC outcomes or examine the role of growth restriction in adverse clinical outcomes in our cohort. Gestational age assessments were obtained by New Ballard score and despite efforts to reduce interobserver variability and generate high quality data, were likely to be inaccurate +/-4 weeks.[158] This reflects the clinical challenges of determining gestational age in low resource settings and the need for improved prenatal and postnatal assessment tools for both clinical prognostication and as research tools to define and understand outcomes for vulnerable phenotypes.

eKMC trial outcomes were limited to 28 days with later follow-up beyond the scope of the PhD. Lack of mid or long-term outcomes, especially on breast feeding practices, growth, neuro-developmental,

audio-visual, and maternal-neonatal mental health outcomes is a key evidence gap from our cohort. Despite extensive understanding of the neuro-developmental sequelae of preterm neonates following HIC intensive care, understanding the trajectory of preterm neonates born in LMIC settings, especially SSA, has received substantially less scrutiny. The INTERBIO-21st Newborn Study observed neurodevelopmental outcomes according to preterm phenotype in a large, multi-ethnic cohort (Thailand, Kenya, Pakistan, Brazil, South Africa, UK) and found that compared to term newborns, preterm neonates were at least twice as likely to score <10th centile for cognition, fine, gross motor and language development, with variability in size of the effect according to the preterm phenotype.[261] Studies exploring the effect of KMC on neurodevelopmental outcomes have been conducted mostly in South America, with a 20-year follow up of clinical trial cohort in Colombia indicating mid-term (1 year) and long-term (20 years) social and behavioural benefits of KMC.[57] To our knowledge, there is no ongoing study evaluating impact of KMC on audio-visual outcomes, which is a significant omission considering an estimated nearly 185,000 preterm neonates develop ROP annually[262] and the extent of auditory impairment following small and sick newborn care has not been fully elucidated in LMICs where lack of ototoxic drug monitoring, deficiencies in jaundice management and prematurity may all contribute to hearing loss. This is an important area for future research, especially for preterm neonates born and cared for in low-resource SSA hospitals.

8.7.2.3 Limitations of PhD objective 3 (Chapter 7)

The main limitations of these exploratory analyses were the post-hoc nature, lack of SGA-specific clinical estimates and inability to adjust for whether KMC was provided at the time of data collection in the analysis. These have already been discussed in Chapter 7 and will not be repeated here.

The role of infections in the causal pathway to mortality were limited by reliance on blood culture data with lack of other investigations to assess host immune response (e.g., CRP, pro-calcitonin), bacterial detection (e.g., PCR screening arrays) or genomic methods of AMR detection. These limitations underline the important infection detection gap which exists in many resource limited settings. Blood cultures are the current gold standard for diagnosing blood stream infections (BSI) yet have low yield with accuracy limited by the need for adequate blood volumes. Blood cultures also typically have a long turnaround time and are expensive. Innovative methods to adapt conventional bacteriology are now commercially available and validation in real-world LMIC settings is warranted. An example is the InTray Colorex pre-prepared media cassettes with ESBL-culture plates which have 60% reduced turn-around-time with comparable sensitivity/specificity compared to conventional bacteriology when piloted in a hospitalised Zimbabwean neonatal population.[263] A shift away from microbiological culture towards more sophisticated host biomarker gene expression is also underway, with the long-term goal of developing a POC test to identify neonatal bacterial infections. Sweeney et al identified an 11-gene diagnostic test (Sepsis MetaScore) with 95% sensitivity and 60% specificity compared to culture confirmed infection, from 3 case-control cohorts (n=213 samples) and including neonates <1500g.[264] Clinical application of such assays is not yet operational, but this is an exciting future prospect. Metagenomic approaches using next generation sequencing to enable rapid bed-side pathogen and AMR detection are also in development. These methods require optimisation of pathways to detect pathogens and distinguish human from bacterial genetic material in a range of clinical specimens before clinical application can be rolled out, but this may be a rapid and reliable tool for neonatal infection and AMR detection in the future.

8.7.2.4 Limitation of PhD as a whole

A limitation of this PhD as a whole is the timing and order of when the research was conducted. An alternative approach would have been to utilise the existing published qualitative evidence for KMC for stable newborns and to conduct the feasibility study after KMC was fully embedded at the trial site. This would have provided a more realistic mortality estimate for the control arm in-order to facilitate appropriate sample size calculation and assessment of RCT feasibility. If the trial was deemed to be feasible, including the perspectives of health workers and families in this formative process could have stimulated more participatory implementation of the intervention, avoiding some of the operational challenges we encountered. A qualitative study could then have been embedded within the RCT to generate novel multi-stakeholder qualitative data regarding early KMC for unstable neonates, alongside piloting of the intervention and data collection tools. Although out with the scope of this PhD, embedding a parallel process evaluation driven by a theory of change and with external social science input, would have generated more robust process and implementation data with value for the field and to understand eKMC trial findings.

Chapter 9 - Implications for policy, programme and research

9.1. Scope of the chapter

This PhD described the work needed to prepare for a clinical trial involving small and sick newborns and provided in-depth understanding of female relative's perceptions of SSNC and KMC. This informed the design of a RCT to investigate the clinical and mortality effects of early KMC for unstable neonates, for which the primary and secondary outcomes findings and an exploratory mechanisms analyses are presented. Since PhD onset there has been a shift in global newborn policy towards greater recognition and promotion of higher quality SSNC as well as substantial disruptions to maternity and newborn health services due to the COVID-19 pandemic. In this chapter I will present an overview of these changes to help understand the PhD findings in light of the shifting global context. I will then synthesise the PhD findings into implications for SSNC, KMC as standard care and early KMC prior to stability from a programmatic and policy perspective along with recommendations for future research priorities to address key evidence gaps (Table 9-1). These implications are drawn directly from the PhD research findings and also indirectly from other literature considered and cited in this thesis. The chapter ends with a conclusion for the whole thesis.

Table 9-1. Policy, programme, and research implications arising from this PhD

PhD objectives & chapters	Policy & programme implications	Research areas to address current evidence gaps
SMALL & SICK NEWBORN CARE (SSNC)		
Obj.1. Understand perceptions of female relatives towards SSNC/KMC (Ch.4)	1. Family-centred care (FCC) model for facility-based SSNC to be implemented at local, national & global levels[a] 2. Enable respectful support for women & families on LMIC NNUs through addressing health systems barriers[a]	1. Implementation research for inclusion of FCC and FIC models on LMIC NNUs, with understanding of perspectives of families (including fathers), health workers & health systems, including cost-effectiveness[a]
Obj.2. Investigate effect of early KMC on survival and clinically important outcomes for unstable neonates <2000g (Ch.5 & 6)	3. High quality SSNC packages to be implemented at scale (e.g., NEST360°), including comprehensive HCW training[a] 4. IPC measures to be scaled up with strengthened AMR surveillance & improved antimicrobial access[b] 5. Core SSNC indicators and quality standards, with national & global tracking through HMIS[b]	2. Innovative solutions to improve small and sick newborn care, including monitoring tools to be developed and validated[a] 3. HAI & AMR acquisition on varied LMIC NNUs to be investigated through improved algorithms, innovative diagnostics & surveillance[b]
Obj.3. Explore pathways to mortality and effect of early KMC on physiological factors (Ch.7)	6. Cause of death attribution and reporting to be strengthened at local & national level, including clinician training and improved tracking[b] 7. Vulnerable phenotype measurement to be improved[a]	4. Prenatal and postnatal tools to assign vulnerable newborn phenotypes to be developed & validated[a] 5. Post-mortem biodata from varied LMIC settings to understand preterm deaths with development of verbal autopsy tools[b]
KMC AS STANDARD CARE FOR STABLE NEWBORNS		
Obj.1. Understand perceptions of female relatives towards SSNC/KMC (Ch.4)	1. Sustainable KMC roll-out to be accelerated in facilities with continuation in community, including female relatives as key stake-holders[a]	1. Family support interventions for KMC to be evaluated, including evaluation of costs to women, families, and society[b]
Obj.2. Investigate effect of early KMC on survival and clinically important outcomes for unstable neonates <2000g (Ch.5 & 6)	2. KMC coverage indicators to be agreed at international level with national & global tracking[b] 3. KMC duration to be optimised within existing KMC programmes[a] 4. Neurodevelopmental and disability screening and follow-up services to be integrated into KMC programmes[b]	2. Determine minimum daily duration of skin-to-skin contact for mortality and other clinical benefits, by vulnerable newborn phenotype[a] 3. KMC duration measurement tools to be developed/ validated[a] 4. Effect of KMC on neurodevelopmental *and* disability mid to long term outcomes to be further investigated[b]
Obj.3. Explore pathways to mortality and effect of early KMC on physiological factors (Ch.7)	5. HCW training and empowerment of KMC providers to promote effective monitoring of stable neonates receiving KMC[a]	5. Explore existing gaps in mechanistic understanding for KMC, especially for infections[a]

PhD objectives & chapters	Policy & programme implications	Research areas to address current evidence gaps
EARLY KMC PRIOR TO STABILITY		
Obj.1. Understand perceptions of female relatives towards SSNC/KMC (Ch.4)	If immediate or early KMC is recommended: 1. An enabling environment for early KMC is to be promoted, including respectful care for women[a] 2. Reduce mother-baby separation through health systems change, with female relative support when mother not available[a]	1. Implementation research for KMC to unstable neonates, including twins and safe delivery alongside other SSNC interventions[a] 2. Understand perceptions of parent/family, health worker and health systems towards KMC prior to stability with linked economic evaluations at each stakeholder level[a] 3. Influence of KMC provider type on clinical outcomes and mechanisms to be further delineated[a]
Obj.2. Investigate effect of early KMC on survival and clinically important outcomes for unstable neonates <2000g (Ch.5 & 6)	3. Criteria for KMC initiation to be defined with international consensus, including "stability" definitions & timing of initiation[a] 4. No recommended policy changes from our trial & additional data needed from level 2/2+ NNUs prior to policy change[a]	4. More evidence for effectiveness and safety of KMC in unstable neonates on level 2/2+ NNUs in resource-limited settings[a] 5. Explore mid- and long-term effects of early KMC on mortality, growth, and neurodevelopmental outcomes[a]
Obj.3. Explore pathways to mortality and effect of early KMC on physiological factors (Ch.7)	5. Adequate clinical monitoring for all unstable neonates +/- KMC with international consensus on temperature, glucose & SpO_2 thresholds[b] 6. Feeding/nutritional support for unstable neonates to be optimised with accelerated roll-out of human donor milk banks and operationalisation of parenteral nutrition where safe and feasible[b]	6. Identification of optimal feeding/nutritional strategies for unstable neonates on LMIC NNUs[b] 7. Mechanisms of KMC in unstable neonates to be explored further, especially stress, epigenetic and neurological pathways and accounting for complexity of clinical effects and interactions[a]

a) Implication arising directly from findings of the research detailed in this thesis; b) Implication arising from other literature considered in this thesis
Abbreviations: AMR = Antimicrobial resistance; Ch = Chapter; FCC = Family centred care; FIC = Family integrated care; HAI = Hospital acquired infection; HCW = Health care worker; HMIS = Hospital Management Information System; IPC = Infection prevention control; LMIC = low and middle-income country; KMC = Kangaroo mother care; NNU = Neonatal unit; SpO_2 = Oxygen saturation; SSNC = Small and sick newborn care.

9.2. Changes to global small and sick newborn care context since PhD onset

Prior to PhD onset there was an important evidence gap for using early KMC in unstable neonates <2000g, which this PhD aimed to address. This innovative use of an established intervention had the potential to accelerate progress towards achieving the SDG 3.2 target for newborn and child survival and promote a healthy environment for newborns to thrive.

SSNC has become more prominent on the global agenda since 2016, with a greater focus on investing in higher quality inpatient care for the smallest, most vulnerable neonates, including family centred care.[21, 22] This builds on the momentum generated by the Every Newborn Action Plan (ENAP), which set out the first national mortality targets (≤12/1000 deaths/live births by 2030) and concrete goals to improve hospital care of small and sick newborns.[19] More than 90 countries are actively implementing ENAP with tracking co-ordinated by UNICEF. The ENAP Measurement Improvement Roadmap (2015-2020) focused on 10 core indicators of newborn care, including KMC, with a process to define indicators, incorporate into national metrics platforms and conduct research to improve data measurement in routine HMIS.[67] Newly set ENAP coverage targets for the period 2020 – 2025 include a requirement for >80% of districts to have a level 2 SSNC unit by 2030.[21] The WHO report "Survive and Thrive: transforming care for every small and sick newborn", was published in 2019 and maps out a pathway towards meeting the SDG3.2 target by 2030 with emphasis on family-centred, high quality care for 30 million vulnerable newborns through a survive, thrive and transform approach and life-long investment for small and sick newborns.[21] The WHO also recently published "Standards for improving the quality of care for small and sick newborns in health facilities". This document aims to define, standardise and mainstream inpatient care of small and sick newborns, is consistent with the WHO quality of care framework and will be a valuable resource to support enhanced quality of care in the context of universal health coverage.[22] Together, these reports and targets represent a much needed shift in global focus towards the most vulnerable neonates and may catalyse progress at national and global level to facilitate wider availability of higher quality SSNC.

The recent publication of the multi-centre iKMC trial has provided evidence for using KMC in the immediate neonatal period.[64] This is a major development in the global KMC evidence base and signals a paradigm shift towards a more family-integrated approach within SSNC. Additional effectiveness data from level 2/2+ African NNUs is expected from the OMWaNA trial with implementation data and economic evaluations still a critical gap for real-world understanding of how to deliver this complex intervention to the most vulnerable neonates.

The COVID-19 pandemic has had profound implications for SSNC across the world from 2020 onwards and risks reversing hard-won gains in neonatal survival. Neonates have a low risk of acquiring SARS-CoV-2,[265] with limited evidence of vertical and breast-milk related transmission and those infected typically exhibit mild symptoms.[265, 266] However, there is conflicting evidence for the impact of the pandemic and associated societal restrictions on the risk of preterm delivery. A meta-analysis including data from 1100 pregnant women in China, Europe and North America reported a 23% increase in pooled prevalence of premature delivery and hypothesised that causality could be due to worsening of maternal and fetal conditions requiring preterm delivery.[266] In contrast, a large retrospective observational study from China (n=164,000) reported a reduction in moderate-to-late preterm deliveries with no concomitant increase in still-birth rates and the authors

propose multiple aetiologies including reduced exposure to common infectious agents and air pollution as a consequence of strict lockdowns.[267] Also, the indirect effects of COVID-19 on maternal and newborn care services due to health-systems disruption have been substantial, especially in the lowest resource settings. A study in Nepal during the initial pandemic phase and lockdown (Jan - May 2020) reported a 52% reduction in health facility births, 50% increase in the institutional stillbirth rate and and three-fold increase in facility-based neonatal mortality.[268] Deleterious effects on breast feeding,[266, 268] KMC provision[269] and increased separation of newborn and parents[270] have also been reported, with wide-spread disruptions to antenatal, intrapartum and postpartum services,[270] inadequate COVID-19 preparedness and high stress amongst health workers.[269, 270] Researchers have called for prioritisation and protection of KMC services during the pandemic, with modelling estimates that the benefit of universal KMC coverage is 65-fold higher than the mortality risk of COVID-19 for neonates in LMICs.[271]

9.3. Small and sick newborn care

9.3.1 Policy and programme implications

Provision of higher quality SSNC for all vulnerable neonates is foundational for meeting global targets and milestones over the coming decade. As shown in this PhD, substantial reductions of inpatient mortality are possible through implementation of higher quality, recommended SSNC with clinical monitoring an essential component. Family-centred care should be at the core of SSNC, with focus on improved quality of care and monitoring, reduction of HAI risk with improved AMR surveillance and underpinned by strengthened cause of death attribution and reporting, including of vulnerable phenotypes. Core indicators and quality standards for SSNC need to be agreed at international level with tracking through routine HMIS. Each of these areas will be discussed in turn below:

9.3.1.1 Family-centred care at the core of small and sick newborn care

The recently published WHO standards for improving the quality of SSNC recommended that “all carers are enabled to participate actively in the newborns care through family-centred care and KMC…with the right for carers to be involved in decision making” (quality statement 4.3).[22] FCC-models should be incorporated into SSNC programmes at local, national and global health-system levels, with inclusion of family members as indicated by ENAP coverage target 4.[19] Actively engaging HCW in neonatal FCC-models through sensitisation and formal training programmes is key for driving FCC-model implementation[202] and should be prioritised by local and national quality improvement initiatives to improve FCC coverage. Including the voices of parents in SSNC programmes and understanding parental and family’s views and feelings towards their premature infant is vitally important, both to respect and support individual families but also to understand how to provide truly family-centred care. The power of female relatives to effect change within the wider community should also be leveraged to promote family involvement in SSNC, through engagement with women’s or family community groups and community leaders.

9.2.1.2 Enable respectful support for women & families

Integration of FCC-models into SSNC requires addressing health system barriers towards respectful support for women and female relatives within health facilities. Barriers include ensuring adequate WASH facilities,[202] unrestricted access to admitted neonates,[46] privacy for breastmilk

expression/feeding and skin-to-skin contact with respectful and culturally appropriate communication, including for illiterate women.

9.3.1.3 Higher quality small and sick newborn care packages to be implemented at scale

Most neonates die due to provision of sub-optimal basic care[272] and an estimated three quarters of a million neonatal deaths could be prevented by 2030 with scale up of existing evidence based interventions.[21] Our observation of a halving in mortality for neonates <2000g, including 29% reduced mortality risk for trial participants (Chapter 7), underscores the improvements possible with a package of SSNC and enhanced focus on monitoring.

An example of how to implement high quality small and sick newborn interventions at scale is NEST360º (Newborn Essential Solutions and Technologies). This initiative aims to reduce neonatal mortality by 50% in four African countries (Nigeria, Malawi, Tanzania, Kenya) by addressing the leading causes of newborn death in Africa, including complications of prematurity. NEST360º aims to do this through a co-ordinated strategy addressing key gaps in newborn care through introducing a health systems package (Fig. 9-1): 1) Optimising affordable and rugged technologies for newborn care with ongoing maintenance; 2) Comprehensive training package for HCW and engineers on use and maintenance of tools; 3) Data collection for improved quality of care to enable scale up; and 4) Shaping the market for sustainable distribution of technologies through-out African countries.[273]

Figure 9-1. Health systems package within the NEST360º initiative

Source: NEST360º.[273]

NEST360º places a strong emphasis on effective monitoring of thermal control, glycaemic control, respiratory stability and jaundice/anaemia and the evidence generated is expected to catalyse sustainable quality newborn care with policy impact. Existing WHO recommendations for monitoring thresholds (e.g., temperature, glucose, SpO_2) and frequency of monitoring for small and sick

newborns[42] should be promoted through national guidelines with linked HCW training, as highlighted in the NEST360 health system package.

9.3.1.4 Infection prevention control measures to be scaled up, with strengthened AMR surveillance

This PhD shows that even with provision of currently recommended SSNC, inpatient mortality is still high with late-onset infections, especially MDR-GNB, playing an important role in mortality. An improved focus on HAI and AMR reduction is integral to achieving further national and global NMR reductions and reaching the SDG 3.2 targets.[274] HAI risk is also closely aligned to quality of SSNC, with provision of reliable, accessible and functional WASH facilities required to ensure strict infection control for newborns, carers and HCW.[22] Weak or absent infection prevention programmes are a risk factor for HAI, particularly AMR sepsis,[108] with overcrowding, understaffing and sharing/re-use of equipment and consumables important health systems factors implicated in neonatal unit outbreaks.[105] There is an urgent need to scale-up known, effective IPC strategies with linked monitoring and surveillance. Interventions such as increasing hand washing compliance rates, cohort isolation (especially for in-born versus out-born neonates), enhanced environmental (and equipment) cleaning and staff education[105] should be incorporated into local and national SSNC programmes and given high priority on the global agenda.

Neonatal access to effective antimicrobials also needs to be prioritised[274] yet should be balanced against rational antibiotic use as part of antimicrobial stewardship programmes to prevent propagation of AMR on LMIC NNUs. Efforts have been made to risk-stratify antibiotic initiation for preterm neonates in HIC settings, with restriction of antibiotics following elective C-sections without active labour.[275] Similar approaches are needed for LMICs, with rational antibiotic prescribing guidelines at national and global level including consideration of antibiotic susceptibility patterns.[276]

Strengthening laboratory services, including increased access and capacity for molecular typing, is foundational for improved HAI and AMR surveillance.[105] An unexpected benefit of the COVID-19 pandemic has been the strengthening of genomic capacity across SSA, with co-ordinated, continent-wide initiatives to establish genomic hubs and advocacy for smaller-scale local genomic surveillance for outbreaks.[277] This could have translational benefit for other disease outbreaks and surveillance, including neonatal AMR, with enhanced staff training, equipment and reporting systems. Morbidity and mortality due to AMR was recently added to the Global Burden of Disease Study[278] but more efforts are required to include AMR indicators in global and national routine measurement programmes, including for neonates.

9.3.1.5 Core small and sick newborn care indicators and quality standards, with national and global tracking

International agreement on core indicators to measure service readiness and provision of SSNC is central to improving health services. The recently published WHO standards for improving the quality of SSNC are an important development[22] and incorporating these standards within national and global level tracking systems with appropriate, agreed metrics, is important to accelerate improvement and identify areas for targeted effort.

9.3.1.6 Cause of death attribution and reporting to be strengthened

Many neonates who die in LMICs do not receive a death certificate[14] and the causes and contextual factors involved in their deaths are not known.[279] The ENAP Strategic Objective 5 states that "Count every newborn through measurement, programme-tracking and accountability to generate data for decision making and action".[19] This is essential to inform newborn health programme prioritisation, planning, resource allocation and monitoring,[280] as well as contributing to regional and global mortality tracking systems.[279]

More accurate cause of death attribution data is needed, accounting for the complexity and co-morbidity of preterm complications, as well as recognising the multiple interlinked pathways and role of contributory factors such as hypothermia or glycaemic dysregulation. Enhanced clinician training on death certificate completion for neonates, especially preterm neonates, is required at facility level, with focus on improved HMIS data collection and link to perinatal mortality audits.

9.3.1.7 Vulnerable phenotype measurement to be strengthened

As shown in this PhD, differentiating between preterm and term growth restricted neonates is challenging in both clinical and research setting and underlines the need for improved measurement of vulnerable phenotypes with better gestational age/weight specific guidance. There are also different phenotypes within the group of preterm neonates, with idiopathic preterm delivery conferring a different mortality and morbidity risk compared to preterm delivery due to severe maternal or placental conditions.[261]

International agreement on definitions of vulnerable phenotypes with strengthened measurement is a high priority, required for targeted clinical and public health programmes to reduce mortality and improve morbidity in the most vulnerable groups. Global estimates are currently ongoing and a Vulnerable Newborn Measurement Collaborative, including WHO, UNICEF and LSHTM, aims to improve measurement of birthweight and gestational age specific birth estimates across 23 countries and >40 research datasets.[24] Current WHO SSNC guidelines care do not distinguish between preterm and LBW neonates, with growth restriction not addressed.[42] Considering the distinct yet overlapping strategies required for different vulnerable phenotypes, this gap should be addressed in future guidelines, with specific targeted interventions for different vulnerable phenotypes.

9.3.2 Research implications

9.3.2.1 Implementation research for inclusion of family centred care models into small and sick newborn care in resource limited settings

Some aspects of FCC, such as family participation in care, are already informally practised in African health facilities out of necessity due to health system limitations.[204] However, there is a lack of published evidence for implementation methods and adapted models for neonatal-FCC models, particularly in relation to complicated social relationships between parents/families and HCW, which may vary depending on the socio-cultural context. Sarin et al described the implementation of FCC on an Indian level 3 NNU using a conceptual framework including culturally sensitive audio-visual training tools to build parent/family skills in 4 areas: infection prevention control; developmentally supportive care and feeding; kangaroo mother care and home care/danger signs. This was preceded by specific HCW training with focus on communication and facilitation skills.[46] A pilot study from a

South African level 3 NNU used a mixed-methods approach to develop, implement and evaluate FCC as a quality improvement initiative, with main components being: early breastfeeding; early introduction of parents to their infant; open visitation policy and parental involvement in caring activities.[281] Such research should be conducted in varying socio-cultural and economic settings, with efforts to understand barriers and enablers for integration of FCC into SSNC from the perspectives of all stakeholders involved in SSNC, including female relatives and fathers, health care workers (including hospital administrators) and the wider community, including religious and community leaders.

Rich data exists on fathers' perceptions of their role in KMC from European, especially Scandinavian, and American settings[51] but less insights are available from LMIC, especially SSA settings, where gender roles and socio-cultural context differ. Including fathers in future KMC qualitative studies, including for KMC prior to stability, is critical to understand and address barriers and could include participatory research approaches to encourage paternal involvement in KMC programme design.

9.3.2.2 Innovative solutions to improve small and sick newborn care and monitoring tools

As highlighted in this PhD, gaps currently exist in accurate, affordable, and simple to use and maintain technology for optimal SSNC and monitoring in low-resource settings. NEST360^{o} is addressing this gap through technological innovation and in collaboration with UNICEF are developing target product profiles (TPP) for newborn innovations. These TPP propose a set of performance and operational characteristics for 16 newborn products across 6 product categories and include IV syringe pumps which can be used with multiple syringe sizes and glucometers with accuracy at all blood glucose ranges using generic testing strips.[282] New innovations due to be developed by NEST360^{o} include point-of-care (POC) blood pH tests, haemoglobinometers and bilirubinometers suitable for use in LMICs with high accuracy being a central part of the TPP.

The use of point-of-care ultrasound (POCUS) in critical care diagnostics and management has expanded over the past decade and the European Society of Paediatric and Neonatal Critical Care recently published guidelines and recommendations for use of cardiac, lung, vascular, cerebral and abdominal POCUS in critically unwell neonates.[283] The potential for POCUS to improve diagnostics and SSNC quality in LMICs is substantial and development of suitable POCUS technologies and algorithms, linked to training and implementation research, is of high priority. The use of smart phone technology for both POCUS applications and pulse oximetry ("Phone Ox")[284] is also a useful innovation with potential for wide impact in low-resource settings.

9.3.2.3 HAI & AMR acquisition on resource limited neonatal units to be understood with improved diagnostics

Understanding how neonates <2000g acquire AMR carriage and HAI on LMIC NNUs is an important evidence gap to inform prioritisation of existing neonatal IPC strategies and development/implementation of new IPC interventions. Maternal MDR-GNB colonisation has been associated with neonatal MDR-GNB carriage in HIC settings, with an estimated pooled proportion of 27% MDR-GNB transmission from colonised mothers to their newborns.[285] However, this was derived from observational studies in HIC and MIC countries and there is a lack of data from LIC, especially in SSA. Caution should be applied to extrapolating findings from other geographical

regions, with neonatal MDR-GNB acquisition likely to be multifactorial and complex with heterogeneous patterns depending on specific nosocomial contexts and health-systems factors.[108]

Development of better clinical algorithms and feasible, low-cost diagnostic tools to rapidly detect infections are essential for clinical care as well as for AMR surveillance and future IPC research. This PhD identified a need for internationally comparably, standardised definitions for suspected neonatal infections with high sensitivity/specificity and validation in vulnerable phenotypes. Although attempts have previously been made to develop such definitions, suitability for use in the lowest resource settings is currently limited by the lack of access to laboratory or POC investigations. Application of innovative infection diagnostics (e.g., adapted culture methods, host biomarker profiles and metagenomic tests) with high sensitivity, specificity and feasibility for use in a range of LMIC settings are also urgently required for the clinical and research need to identify invasive infection.

9.3.2.4 Innovative tools to assign vulnerable newborn phenotypes

Improved prenatal and postnatal gestational age assessment tools are urgently required which are more suited to LMIC settings, do not require extensive training and give an accurate estimate of gestational age, including distinguishing between growth restricted and appropriately grown neonates. A prenatal innovation currently being evaluated in African settings, including The Gambia, is the TraCer device, a low-cost tablet based POCUS tool which estimates gestation from the trans-cerebellar diameter (TCD) which is highly conserved and growth-restriction resistant.[284] This can be used during all stages of pregnancy and links to standardised INTERGROWTH-21 growth charts for gestational age estimation. Efforts are also underway to use TCD and innovative algorithms to increase the accuracy of late pregnancy ultrasound scanning to improve gestational age estimation for appropriate-for-gestational-age and growth restricted neonates.[286] Innovative tools with potential for postnatal clinical application include smartphone ophthalmoscopy to assess the blood vessel development at the back of the newborn eye[287] and evaluation of the newborn metabolic profile through dried blood spot tests.[288] Clinical validation and application of these tools will enable provision of targeted antenatal and postnatal interventions (e.g. corticosteroids), as well as more accurate cause of death attribution and surveillance. They are also valuable research tools for future clinical trials evaluating interventions to improve gestational-age specific outcomes in resource limited settings.

9.3.2.5 Post-mortem biodata to understand pathways to mortality for neonates <2000g

As shown by our conceptual framework (Chapter 7), pathways to mortality for these newborns are complex with multiple interlinked factors. A more nuanced understanding of how and why preterm and growth restricted neonates die is required, especially to quantify the contribution of infections and AMR. The Child Health and Mortality Prevention and Surveillance (CHAMPS) Network collects standardised, population-based, longitudinal biodata from a network of high mortality burden African and South Asian sites and includes children and neonates of all gestations and weights. The innovative methods include minimally invasive tissue sampling with genomics, histopathology and immunohistochemistry and linkage to verbal autopsy and antemortem clinical data.[85] Over time CHAMPS is expected to provide detailed insights into mortality pathways for neonates <2000g with a clear link to policy and plans to strengthen verbal autopsy tools.

9.4. Kangaroo mother care as standard care for stable newborns

9.4.1 Policy and programme implications

9.4.1.1 Sustainable kangaroo mother care roll-out in health facilities to be accelerated

The work presented in this PhD underlines an urgent need to accelerate scale-up of facility initiated KMC in LMICs, especially in SSA. The continuation of KMC along the spectrum from health facility to community is also an important aspect of policy to be addressed. The ENAP targets state that ≥75% of stable newborns <2000g should receive KMC by 2025.[19, 21] Although many LMIC countries are making progress, implementation is limited with low-coverage in the highest burden countries.[289] Of 90 countries reporting data for the ENAP targets, only 31% reported having a KMC policy or guideline in place in 2018,[290] highlighting the substantial progress required if the ENAP quality of care milestone is to be met before 2025. UNICEF already supports 25 high mortality burden countries with KMC implementation, mostly in Africa and Asia, and further collaboration among national, public, and private partners is required along with appropriate budget allocation, advocacy messaging and community participation. Robust implementation evidence already exists for KMC in stable newborns[62, 291] and further implementation research by the KMC Scale Up Study Group is ongoing for district-level models of hospital scale-up with continuation in the community in India and Ethiopia.[289]

Ample evidence exists that roll-out of facility-based KMC programmes in SSA requires good support of mothers, both by adequately trained HCW,[51] KMC provider peers[292] and families.[47] However, in-order to enable these stakeholders to support mothers, policy makers and KMC programmes need to prioritise the mitigation of health-systems barriers. Addressing staff shortages so enough trained HCW are available to support mothers and avoiding intra-departmental staff rotations and attrition with loss of experienced HCW is foundational for KMC support. Promoting KMC champions at all health-systems levels and facilitating supportive supervision and mentoring are also key.[47] Mitigating the financial impact of prolonged hospitalisation and transportation costs,[191] loss of livelihood and impact on domestic and agricultural responsibilities through incentivisation schemes or task-shifting within the extended family may also enable more family support.

This PhD was mostly focused on facility initiated KMC, with limited consideration of KMC continuation in the community post-discharge or community-initiated KMC. However, a recent systematic review and meta-analysis reported a high certainty of evidence that community KMC reduces neonatal mortality for all neonates <2500g, based on two trials in rural/semi-rural India and Bangladesh.[293] Our finding that Gambian female relatives are willing to support KMC post-hospital discharge, with potential for task-shifting around women's agricultural and domestic responsibilities, underlines the need to incorporate these family members into community KMC programmes.

9.4.1.2 Kangaroo mother care coverage indicators to be agreed with national & global tracking

Development of KMC process, outcome and impact indicators with integration into national and global measurement systems is an essential aspect of global KMC scale-up. However, defining coverage indicators for KMC is complex as the intervention involves several components delivered over time both within hospitals and post discharge, as well as subjective determination of "stability"

in the absence of standardised definitions. The Every Newborn measurement improvement roadmap aims to address these metric gaps, with a WHO-LSHTM led, multi-stakeholder approach to defining Every Newborn core indicators, including for KMC, and based on evidence for optimal measurement method and indicator validation. The EN-BIRTH KMC-validation study assessed the validity of KMC coverage measurement in Tanzania, Nepal and Bangladesh and identified that KMC coverage of admission to KMC wards/corners had high sensitivity in KMC registers with potential for aggregation into routine HMIS to track coverage.[67] Defining effective coverage (i.e., high quality KMC) is another key gap for policy and would benefit from further research to validate measurement methods and metrics of what constitutes high quality KMC.

9.4.1.3 Kangaroo mother care duration to be optimised

Multi-stakeholder perspectives on barriers for KMC delivery are well known[47, 51, 191] and should be mitigated in existing KMC programmes to promote longer time spent in KMC position to achieve the currently recommended duration ("for as long as possible").[42] Harmonised guidelines are required for KMC implementation at all health facility levels and should include detailed guidance about how to achieve longer durations through provision of a comfortable environment (e.g., beds, mosquito netting, recreational activities) whilst ensuring that mother's and families' basic rights for respectful care are met. Understanding and addressing local barriers to providing prolonged KMC is key with mitigation through a multistakeholder and locally driven approach, using quality improvement methods (e.g., Plan-Do-See-Act) where possible. Optimal KMC duration and methods for reliable measurement of KMC duration are key evidence gaps, but this should not limit or delay programmatic efforts to increase KMC duration.

9.4.1.4 Neuro-developmental screening and follow-up systems integrated into kangaroo mother care programmes

Adverse neurodevelopmental outcomes and disability are high risk for neonates <2000g and programmatic/policy change is required to integrate screening and follow-up systems into existing programmes. This is a high priority at local and national level with global advocacy needed for neuro-developmental screening and treatment programmes, especially for ROP which affects an estimated 184,700 neonates a year with high risk of visual impairment.[262] This has been a previously under-prioritised aspect of hospital-based KMC programmes yet is important to capitalise on KMC as an "entry-point" for improved SSNC. Likewise, early detection of neurological impairment through targeted screening at KMC follow-up clinics with linkage to early childhood intervention programmes for survivors of preterm birth would enhance the post-neonatal care and childhood outcomes for these vulnerable neonates.

9.4.1.5 Health care worker training & kangaroo mother care provider empowerment central to clinical monitoring

Enhanced monitoring by KMC providers is integral to KMC practice, with potential for early identification of illness and empowerment of the KMC provider as main carer. However adequate counselling of mothers and other family members providing KMC is still required to ensure they have the knowledge and skills to provide effective monitoring. This informal monitoring should also be complemented by vital sign and temperature spot checks as per recommendations for high quality SSNC.[22] Ensuring minimum monitoring standards are met entails a substantial investment of

material resources, human resources and health systems change including targeted HCW training to recognise the significance of abnormal physiological parameters and enable rapid corrective action.

9.4.2 Research implications

9.4.2.1 Family support interventions to be evaluated, including economic insights

Further research is needed to design and evaluate interventions to promote family support and involvement in KMC programmes. Such studies could draw on interventions used in other maternal and newborn health spheres to encourage health service utilisation, such as demand-side financing interventions (cash-transfer and vouchers).[294] Participatory co-design of interventions is key for long-term uptake and should be encouraged where possible in study designs with input from all family members involved in newborn care decision making. Understanding the financial implications of providing facility-based KMC for women, families and households is a research priority, with an urgent need for cost-effectiveness estimates for different health system levels.

9.4.2.2 Determine the minimum duration of skin-to-skin contact needed for benefit

The most recent WHO guidelines for preterm neonates recommends providing "as close to continuous KMC as possible" and highlighted the evidence gap for minimum duration per day that skin-to-skin contact is needed for survival and other important clinical effects.[42] This was also highlighted by the most recent Cochrane review and would fundamentally inform KMC policy and programmes and enable benchmarking as part of national and global tracking. Future research should also explore the minimum duration needed for each KMC session, which will help to inform duration of skin-to-skin contact sessions and contribute towards a more evidence based definition of intermittent KMC.

9.4.2.3 Kangaroo mother care duration measurement tools to be developed and validated

Improved tools to accurately measure duration in KMC position are needed for both facility and community KMC practice, to inform measurement of effective coverage, ensure duration targets are met within programmes and for use as research tools. Routine registers or population-based surveys are likely to be unfeasible[67] for this purpose and more research is required to validate KMC provider and HCW methods of recording duration as well as innovations such as smartphone apps or KMC position sensors or other wearables.

9.4.2.4 Neurodevelopmental mid to long-term outcomes to be evaluated

Evaluation of short-term and long-term neurodevelopmental and disability outcomes, including neuro-imaging, for effect of KMC is a research priority. Data from varied settings, especially Africa and Asia, are required to characterise the trajectory of neurodevelopment following preterm or LBW delivery with characterisation by vulnerable phenotype. Alongside this baseline understanding, exploration of KMC effects on neurodevelopment, behaviour, social-communication, audio-visual outcomes, and mental health are a high priority. This is needed to inform clinical care, policy/programme and to provide a baseline for evaluation of other neuro-protective interventions which could be co-administered before or alongside KMC.

The OMWaNA trial includes a secondary outcome of "presence and severity of IVH up-to 7-days and late intracerebral sequelae of prematurity at 28-30 days", measured with cranial ultrasound.[65] This

will give important insights into both prevalence of neurological sequelae in the control arm and effect of KMC on short-term neurological changes. Detailed insights into KMC effects on short term functional brain maturation and mid-term (12-24 months) neurodevelopment, mother-infant interaction and neuro-endocrine response systems will also be provided by the IPISTOSS trial, conducted in Scandinavia,[295] with generalisability of some outcomes to LMIC settings. Future research in LMICs should also evaluate effects of KMC on audio-visual impairment, school readiness and childhood behaviour.

9.4.2.5 Explore gaps in mechanistic understanding of kangaroo mother care, especially infection effects

Understanding the infection prevention mechanisms of KMC is a current evidence gap, with data needed from both HIC and lower-resource settings, to understand whether the context of IPC and HAI influences the effect of KMC on infection risk. Future research should include genomic methods for insights into how varied neonatal microbiota (skin/intestine/respiratory) evolve over time in relation to the KMC provider microbiome and duration of KMC provided, as well as whether KMC influences the transmission dynamics of AMR pathogens. This would aid understanding of KMC mechanisms, with translation to improved infection prevention strategies. The IPISTOSS trial is planning to explore the effect of KMC on neonatal microbiome in a HIC setting, with 2-year follow-up.[295] The biological skin and rectal/recto-vaginal samples from paired neonate-KMC provider dyads collected during eKMC trial may also provide valuable insights into this area.

9.5. Early kangaroo mother care prior to stability

9.5.1 Policy and programme implications

9.5.1.1 Promote an enabling environment for early kangaroo mother care prior to stability

As indicated in this PhD, provision of early KMC to unstable neonates is feasible at scale only with provision of an enabling environment for mothers and family members to be continuously present on NNUs. Key aspects of promoting an enabling environment include: comfort; space; safety (woman and neonate); privacy; patient flow; access to WASH facilities and protection from HAI; access to a safe, clean place to eat and maternal access to health care. These factors should be addressed in any future KMC implementation guidelines if there is a change in global KMC policy and may entail substantial investment in infra-structure (e.g., establishment of additional mother-baby units) as well as material (e.g., beds) and human resources. This is important to meet the rights of the women to dignified and respectful care as well as to practically deliver KMC to unstable neonates. The impact of any future policy changes on other admitted neonates and their families should also be considered, especially to prevent HAI and ensure equitable access to care.

9.5.1.2 Reduce mother-baby separation through health systems change

If immediate or early KMC is recommended in international policy as standard care for unstable neonates there needs to be a shift in culture and health systems towards managing the “mother-newborn” dyad as opposed to existing siloed approaches to maternal and neonatal care.
As illustrated by the iKMC trial, this will require an inter-speciality collaborative approach to providing KMC to unstable neonates with joined up thinking about provision of concurrent obstetric and neonatal care and the impact of continuous KMC on maternal physical and mental health. This

should also be considered in the context of the COVID-19 pandemic with efforts to "Keep mums and babies together" as the standard care, even for unstable vulnerable neonates.

9.5.1.3 Criteria for kangaroo mother care initiation to be defined with international consensus

International level consensus is required for determining when KMC should be initiated and should include standardised stability definitions suitable for the most resource-limited settings. The findings of all KMC trials exploring use of KMC in unstable neonates should be considered during guideline development, including the eKMC trial,[206] iKMC trial[64] and the OMWaNA trial when results are available.[65] Clear guidance for when to start (and stop) KMC in unstable neonates is essential to support clinical decision making and to avoid potentially harmful practices such as prioritisation of KMC over other essential interventions.

9.5.1.4 No recommended kangaroo mother care policy changes for level 2/2+ neonatal units

I cannot recommend any change to international KMC policy for standard care of unstable neonates managed on resource limited level 2/2+ NNUs, based on the eKMC trial findings. The iKMC trial finding of a 25% mortality reduction for neonates 1 to <1.8kg on level III LMIC units, has important policy and programmatic implications, but considering the implementation challenges, substantial health systems shift required, and vulnerable population involved, we advise caution in extrapolating iKMC results to all LMIC NNU settings without additional data from level 2/2+ units. The OMWaNA trial will provide more clarity on this priority question with results expected in 2022. If policy change is recommended in response to the iKMC trial findings, care should be taken to represent only the iKMC trial population in any future guidelines, as the effectiveness and safety of immediate or early KMC in ELBW and extremely premature neonates has not been demonstrated.

9.5.1.5 Ensure adequate clinical monitoring for all unstable neonates +/- kangaroo mother care

Adequate clinical monitoring of thermal control, glucose control and stability markers is needed for all unstable neonates, especially those receiving KMC, to ensure timely detection of illness and detection of abnormal physiological signs. KMC programmes which include KMC for unstable neonates in the future should ensure adequate pulse oximetry monitoring as a minimum standard, with frequent temperature and glucose monitoring embedded into clinical care. International consensus on standardised definitions and thresholds for temperature, glucose and SpO_2 levels are required to enable benchmarking of quality at national and global level.

9.5.1.6 Optimise feeding/ nutritional support for unstable neonates

Optimal nutrition is essential for neonatal survival as well as promoting growth, immunity, and longer term neurodevelopmental and metabolic outcomes. KMC has the potential to positively impact nutrition through promotion of breastmilk feeding, but early KMC may not be sufficient to achieve optimal nutrition if provided by non-maternal KMC providers or in settings lacking currently recommended feeding/nutritional support for unstable neonates (e.g., donor milk banks, parenteral nutrition).

Promotion of known strategies to improve nutrition of high risk neonates <2000g are required in national and global policy, including more focused attention on aspects of "KMC nutrition" which is a relatively neglected component of KMC practice. National policy and programmes which address local barriers to providing human donor milk and build capacity for sustainable donor milk banking

are recommended and would contribute towards improving nutritional management alongside KMC. Operationalising safe parental nutrition is also required to meet WHO quality standards and to ensure that all vulnerable neonates have safe access to this essential nutritional treatment. Comprehensive guidance is required by health-systems level, ideally based on a framework for establishing and monitoring parenteral nutritional support, as previously suggested for use in LMIC paediatric oncology services.[236] Other components of nutrition should also be optimised within national programmes, such as iron, vitamin D, calcium, and phosphorous supplementation, which are all WHO recommended[42] yet inconsistently provided.

9.5.2 Research implications

9.5.2.1 Implementation research for immediate/early kangaroo mother care for unstable neonates

If immediate or early KMC in unstable neonates is included in international policy, implementation research is urgently needed to understand how to safely roll-out this intervention, including economic evaluations. Methods to evaluate immediate/early KMC implementation as a complex intervention should be used, as per existing guidance[50] and utilising appropriate study design and analytical approaches including rigorous process evaluation methodology.

Understanding perceptions of the spectrum of stakeholders likely to be involved in providing immediate/early KMC to unstable neonates is central, with parents, families especially female relatives, and health workers at the core. Understanding the views of the wider community/society is also important, especially community women's groups and religious leaders. Understanding how to provide KMC to unstable twins simultaneously is a current gap and warrants targeted research to understand the specific barriers. Mothers provided most KMC to unstable neonates in the OMWaNA feasibility study[153] and iKMC trial[64] and as shown by both the iKMC and eKMC trials, absence of the mother during the initial 24h of neonatal care is an important barrier to delivering the intervention. Understanding how to address this implementation gap whilst also ensuring adequate and respectful care for mothers and female relatives is critical. Future research to explore family members perceptions of KMC in unstable neonates should also focus on KMC feeding practices, which are inherently different for female relatives compared to mothers and which may adversely impact on KMC nutrition for unstable neonates.

Understanding how to safely deliver KMC to unstable neonates alongside other SSNC interventions is a research priority. Understanding the perceptions and attitudes of HCW, especially nurses', towards the intervention is foundational for effective implementation due to the prominent supportive and authoritative role which nurses play on NNUs in all settings.

Economic evaluations to understand incremental costs for women participating in immediate or early KMC is needed, as is understanding house-hold cost implications. Understanding the infrastructure and health systems changes needed to implement KMC for unstable neonates is also required, with consideration of costs, IPC and enabling a FCC approach. The iKMC trial have already started this through the establishment of mother-NICUs and further details into how this was achieved are awaited. The OMWaNA trial will also conduct novel economic evaluations, including cost-effectiveness, incremental cost, budget impact and equity of KMC before stabilisation relative to standard care, from Ugandan provider and household perspectives.[65]

9.5.2.2 Influence of KMC provider type on clinical outcomes and mechanisms

The existing evidence for KMC outcomes and mechanisms is focused mostly on mothers, less so on fathers and there is a gap for other relatives. Understanding whether the type of KMC provider is important for clinical outcomes is important to inform policy and programme priorities and define the role of family support in KMC provision more clearly for both stable and unstable neonates. Key questions include the effect of KMC provider type on mortality risk, feeding/growth outcomes, and infection risk. Considering the spectrum of KMC providers with high rates of non-maternal KMC provision observed during the eKMC trial, we are uniquely placed to conduct further mechanistic analyses using eKMC trial data and stored biological samples to give insight into these questions.

9.5.2.3 More evidence for effectiveness and safety of kangaroo mother care in unstable neonates on level 2/2+ NNUs

Although the iKMC trial provides evidence for mortality effect of immediate KMC in level 3 NNU settings in India and SSA, important questions still exist about effectiveness and safety in settings with lower levels and quality of SSNC. The multicentre OMWaNA trial is ongoing, with results expected in 2022. The four Ugandan sites are comparable to the eKMC site in terms of respiratory support (bCPAP only), baseline mortality rates and aim to start KMC within 48h of delivery. The eligibility criteria, outcomes and design were purposefully similar to eKMC to enable pooled analyses (Table 1-2) and a target sample size of 2,500 should provide adequate power to detect a mortality difference.[65] Understanding the effect of early KMC in ELBW neonates (<1kg) through pooled eKMC-OMWaNA analyses will also provide valuable insights into weight-specific mortality effects. OMWaNA will be an important addition to the evidence base for KMC use in unstable neonates and may also provide insights into the optimal timing of initiation and minimum duration of skin-to-skin contact needed for mortality and clinical effect.

More data on the safety of KMC in unstable neonates is needed for operationalisation of the iKMC trial findings. A mixed-methods approach is recommended, to gain both in-depth understanding of maternal/family safety concerns and HCW observations which can identify potential safety gaps.

9.5.2.4 Explore mid and long-term effects of early kangaroo mother care on mortality, growth, and neurodevelopment

Both iKMC and eKMC trials focused on the short-term effects of immediate or early KMC, as does the OMWaNA trial. Expanding the follow-up of the trial cohorts to explore mid-longer term effects on mortality, growth and neurodevelopment is required, especially as out of hospital mortality for these vulnerable neonates in LMIC settings may be high and under-recognised in the absence of formal follow-up systems.

9.5.2.5 Identification of optimal feeding & nutritional strategies for unstable neonates on resource limited neonatal units

Neonatal feeding and nutritional strategies for preterm/VLBW neonates in HIC settings are becoming more evidence based,[150] yet there is an evidence gap for LMIC settings, especially SSA,[229] where variations in clinical care and monitoring require different approaches. Gaps exist in knowing when to safely start feeds in neonates <2000g, how quickly to increase feed volumes, how to feed via gastric tube (e.g., continuous versus bolus) and the use of micronutrient and prebiotic milk fortifiers.[229] Pragmatic feeding interventions identified as being potential candidates for future LMIC trials include higher starting volumes, rapid feed progression and use of breast milk fortifiers. A core outcome set

for future neonatal nutritional interventions is also recommended and should include long term growth and neurodevelopmental outcomes. Understanding barriers to safe parenteral nutrition use with linked research to enable exploration of feasibility in different LMIC settings is also vital to accelerate progress towards future scale-up.

9.5.2.6 Mechanisms of kangaroo mother care in unstable neonates to be explored further

The exploration of early KMC effect on physiological factors presented in this thesis gives only limited insights into possible mechanisms and amelioration of pathways to mortality. Further insights are expected from the iKMC, OMWaNA and IPISTOSS trials and more understanding of physiological mechanisms should include technological innovations such as NIRS and heart rate variability tools.

9.6. Conclusion for the PhD

This PhD investigated the mortality and clinical effects of early KMC for unstable neonates <2000g in The Gambia in the context of wider SSNC and KMC in low-resource settings. I presented qualitative and quantitative data, including the results of a RCT which has provided valuable insights and novel data regarding the effectiveness, feasibility and realities of providing early KMC to unstable newborns in a resource limited level 2/2+ NNU in West Africa.

Nearly 2.5 million neonates died within the first 28 days after birth in 2018, of which 80% were LBW and 66% were born preterm.[12] SSA has the highest crude neonatal deaths and neonatal mortality rates globally,[12] with the second highest proportion of global preterm births.[32] Neonatal mortality is 10-fold higher in The Gambia (26.3/1000 live-births) compared to UK (2.6/1000 live-births),[12] and urgent focus is required to reduce inequalities in mortality risk and ensure that no newborn is left behind. The impact of being born preterm, with or without growth restriction, also goes beyond survival with an estimated 1 million small and sick newborns surviving with a long-term disability.[296] This has huge psychological, emotional, practical, and financial implications for neonates, parents and families, as well as substantial impact on health systems and societies with loss of human potential for life-long health and wellbeing.

There has been recent progress in many countries towards meeting the global target of $\leq$12 deaths/1000 livebirths by 2030 (SDG3.2) but >60 countries are not currently on track to meet the target[21] and the COVID-19 pandemic threatens to reverse gains. Up-to 30 million neonates require hospital care annually and improving the quality of this care is key to reaching global targets. Universal coverage of high quality SSNC, including KMC for stable newborns, has the potential to save 747,400 lives, if provided at scale.[21, 89]

The work conducted as part of this PhD demonstrates that inpatient mortality of neonates <2000g can be reduced in a relatively short time through provision of recommended SSNC interventions and KMC, with close clinical monitoring central to improved quality care. Promotion of a family centred approach to SSNC on a resource-limited NNU is feasible and essential for KMC provision in West African and should be embedded into SSNC policy and programmes with linked implementation research. Neonatal HCW are central to providing improved SSNC and newborn outcomes, with a critical need to address health systems barriers to ensure sufficient numbers, adequate training and retention of neonatal trained HCW within public health systems.

Despite robust evidence for KMC and decades of implementation, there are key evidence gaps for optimal KMC dose for clinical benefit, effects of non-maternal KMC providers and feasible, family-centred methods of achieving prolonged duration in KMC position. Many questions persist around how KMC exerts a positive clinical effect, especially the infection prevention effects, feeding practices/nutrition and long-term sequelae, the results of which could translate to inform clinical practice. The vast majority of neonatal trials take place in HIC settings, with a strong track record of high quality evidence to inform clinical decision making and improve outcomes for vulnerable neonates.
There is a crucial need for more low-cost, high-benefit feasible interventions addressing local health needs and targeted at vulnerable phenotypes, focused on feeding, nutrition and preventing HAIs. These should be evaluated in a range of LMIC hospital settings, recognising the heterogeneity which exists in resource-limited settings to inform local and regional public health policy and programmes. The infection detection gap must be closed, through innovative science and technology. This is critical for clinical care and evaluation of IPC interventions, but also to enable antimicrobial stewardship and attempt to stem the tsunami of AMR on neonatal units. Innovative approaches are also required for neonatal emergency-care trials investigating time-critical interventions in LMICs, with focus on empowering meaningful and informed family participation in future trials, including family-driven outcomes.

KMC is integral to higher quality SSNC but should not be considered as a stand-alone intervention. KMC is an entry point for family-centred care, exclusive breast milk feeding and enhanced monitoring and thermal control, but for optimal neonatal outcomes the other aspects of SSNC need to be strengthened in parallel. Operationalising SSNC and KMC requires more than lip service attention to families and respectful care. Meeting all the needs (including medical and psychological) of mothers and female relatives, with inclusion of fathers where possible, is foundational for effective KMC to be provided, including for prolonged KMC duration and prior to stability. A shift to immediate or early KMC for unstable babies may have limited impact if the rest of SSNC is weak and a holistic approach to improving quality of hospital care of the small and sick newborn is urgently needed. Addressing IPC gaps is critical to prevent HAI, ensure preterm survival and promote long-term neurodevelopmental outcomes for preterm survivors. Infections with highly pathogenic AMR bacteria are devastating for the preterm newborn, their families and the HCW who strive hard to look after them and it is imperative to understand, address and mitigate invasive hospital acquired infections. Equally, optimising the quality of thermal and oxygen care of newborns in resource limited hospitals is foundational for better preterm outcomes and achievable with existing technology, including prolonged use of KMC after stability. This research has highlighted that improving the quality of existing SSNC is high priority for level 2/2+ NNUs, before expanding to level 3 or introducing complex interventions such as immediate or early KMC for unstable neonates.

In summary, to achieve improved neonatal survival and reduce long-term morbidity for all small and sick newborns we need to take a more holistic approach to providing high quality hospital newborn care, with KMC at the heart, and working closely with mothers, fathers, and families in equitable partnership. Addressing avoidable causes of neonatal mortality through improved SSNC and implementation of known, effective interventions at scale should be a public health priority, worthy of additional investment and targeted programmatic focus. More carefully designed, rigorous neonatal trials and implementation evidence is urgently needed with participation of families and

front-line HCW integral to developing feasible, low cost interventions which address the local neonatal health needs and will help to move forwards towards reducing avoidable neonatal mortality in all settings.

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11. Annexes

A-1. Regulatory approvals
- A-1-1. Feasibility study ethical approval: LSHTM Observational Ethics Committee
- A-1-2. Feasibility study ethical approval: GG/MRCG Joint Ethics Committee
- A-1-3. Feasibility study Gambian Government Ministry of Health approval
- A-1-4. Qualitative study ethical approval: LSHTM Observational Ethics Committee
- A-1-5. Qualitative study ethical approval: GG/MRCG Joint Ethics Committee
- A-1-6. Qualitative study: Study site (EFSTH) approval
- A-1-7. eKMC trial ethical approval: LSHTM Interventional Ethics Committee
- A-1-8. eKMC trial ethical approval: GG/MRCG Joint Ethics Committee
- A-1-9. eKMC trial Gambian Government Ministry of Health approval
- A-1-10. eKMC sponsors agreement: LSHTM

A-2. PhD timeline with key milestones as per PhD objectives

A-3. Environmental surveillance results at eKMC trial site (May 2018 – December 2019)

A-4. Supplementary material for published article 1 (Ch.4; Qualitative study of female relatives)
- A-4-1. In-depth interview guide
- A-4-2. KMC information sheet
- A-4-3. Standards for reporting qualitative research (SRQR) checklist

A-5. Supplementary material for published article 2 (Ch.5; eKMC trial protocol)
- A-5-1. aSCRIP definition
- A-5-2. SPIRIT checklist

A-6. Supplementary material for published article 3 (Ch.6; eKMC trial findings)
- A-6-1. eKMC trial Statistical Analysis Plan
- A-6-2. Supplementary tables and figures
- A-6-3. CONSORT checklist for reporting of eKMC trial

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Observational / Interventions Research Ethics Committee

Dr Helen Brotherton
LSHTM

27 February 2017

Dear Helen,

Study Title: An investigation of early kangaroo mother care for hospitalised neonates weighing <2000g in The Gambia: A feasibility & acceptability study

LSHTM Ethics Ref: 11887

Thank you for responding to the Observational 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
Local Approval	GG:MRC EC approval letter	12/10/2016	1.0
Investigator CV	S Cousens	19/10/2016	1
Investigator CV	H Brotherton	19/10/2016	1
Investigator CV	CV Joy Lawn	19/10/2016	1
Investigator CV	S Zaman	24/10/2016	1
Protocol / Proposal	Clinical record form V2	14/12/2016	2.0
Information Sheet	Study 1 consent information sheet.V4.141216	14/12/2016	4.0
Information Sheet	Study 2 consent information sheet caregivers V4.141216	14/12/2016	4.0
Information Sheet	Study 2 consent information sheet HCW. V4.141216	14/12/2016	4.0
Protocol / Proposal	Cover letter detailing responses to EC decision	14/12/2016	1.0
Information Sheet	Study 1 consent information sheet.V5.020217	02/02/2017	5.0
Protocol / Proposal	Protocol V2 020217	02/02/2017	2.0
Covering Letter	Cover letter detailing clarifications 15.02.17	15/02/2017	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.

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,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
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The Gambia Government/MRC Joint
ETHICS COMMITTEE

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12 October 2016

Dr Helen Brotherton
London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT, UK

Dear Dr Brotherton

SCC 1503v2, A feasibility study for a randomised controlled trial investigating early kangaroo mother care in hospitalised neonates weighing <2000g

Thank you for submitting your response letter dated 11 October 2016 addressing the issues raised by The Gambia Government/MRC Joint Ethics Committee at its meeting held on 2 September 2016.

Your responses are quite satisfactory. This project has now received full ethical approval.

With best wishes

Yours sincerely

Mr Malamin Sonko
Chairman
Gambia Government/MRC Joint Ethics Committee

Documents submitted for review:-

- Response letter – 11 October 2016
- EC reply letter – 27 September 2016
- SCC application form, version 1.0 – 18 July 2016
- Informed Consent Document (for child, HCW, parent), version 1.0 – 18 July 2016
- Questionnaires (parents/neonatal health-care workers), version 1.0 – 18 July 2016
- CVs:Helen Clare Brotherton; Elio Cesar Quesada Gonzalez; Christian Bottomley; Joy Elizabeth Lawn
- Letter of support from MOH&SW

REPUBLIC OF THE GAMBIA
MINISTRY OF HEALTH & SOCIAL WELFARE
THE QUADRANGLE
BANJUL
Tel: 4227300/4227301 Fax: 4229325

Ref: DHS/AD/2016/01 **13th July, 2016**

Dear Dr. Brotherton,

A FEASIBILITY STUDY FOR AN RCT INVESTIGATION BENEFITES OF KANGAROO MOTHER CARE IN MODERATELY UNSTABLE HOSITALISED NEONATES WEIGHING < 2000G.

After carful scrutiny with the pertinent staff of the Edward Francis Small Teaching Hospital (EFSTH) and the Ministry, we are pleased to inform you that approval has been granted for your above study.

We will be happy to support you whilst you conduct this study with the EFSTH.

Please accept the assurances of my highest consideration and esteem.

Yours sincerely,

Dr. Samba Ceesay
Acting Director of Health Services

Cc: Permanent Secretary- MoH&SW

Files

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

MSc Research Ethics Committee

Ms. Maura Daly
MSc Student
Public Health in Developing Countries
LSHTM

21 June 2017

Dear Maura ,

Study Title: Acceptability of Female Family Members as Potential Substitute Kangaroo Care Providers in The Gambia

LSHTM MSc Ethics Ref: 12398

Thank you for your application for the above MSc research project, which has now been considered by the MSc Research Ethics 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, 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.

You state that you will delete the audio recordings once the transcription is complete. The audio files cannot be stored on the digital recorder unless it is encrypted. If you cannot access an encrypted recorder please ensure that the audio recordings are moved to the encrypted USB drive following the interview and then immediately deleted from the digital recorder.

Approved documents

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

Document Type	File Name	Date	Version
Investigator CV	MdalyLMCV	06/03/2017	1
Local Approval	RCH unit letter 1	19/03/2017	1
Protocol / Proposal	KMCprotocol_MDALY	23/03/2017	3
Information Sheet	KMC-consent-DALY	20/04/2017	2
Protocol / Proposal	KMC_IDI guide_MDaly	20/04/2017	2
Local Approval	SCC 1535v1.1_Daly_Approved_21Apr17	06/05/2017	1
Covering Letter	LSHTMKMCCoverletter6:5:17	06/05/2017	1
Protocol / Proposal	KMCprotocol_MDALY 6:5:17	06/05/2017	4
Covering Letter	CAREcoverJune5	05/06/2017	2
Protocol / Proposal	KMCprotocolJune3	05/06/2017	5

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: http://leo.lshtm.ac.uk .

Yours sincerely,

Dr Cicely Marston
Chair

Maura Daly
Flat 9 Rosslyn Court, 10 Ornan Road
London, UK NW4PU

21 April 2017

Dear Maura Daly

SCC 1535v1.1, Acceptability of Extended Female Family Members as Potential Substitute Kangaroo Care Providers in The Gambia

Thank you for submitting your revised proposal dated 16 April 2017 addressing the issues raised by the SCC at its meeting held on 3 April 2017.

I am happy to provide full SCC approval for this project whcihc will be forwarded to the Ethics Committee for further consideration at their next meeting on 28 April 2017.

With best wishes

Yours sincerely

Dr Anna Roca
Acting Chair, Scientific Coordinating Committee

Cc Dr Helen Brotherton

Documents submitted for review:

- SCC application form, version 1.1 – 21 April 2017
- Resposne letter – 18 April 2017
- Protocol, version 1.0 – 20 March 2017
- Indepth interview guide, version 1.0 – 20 March 2017
- Informed Consent Document, version 1.1 – 16 April 2017
- EFSTH letter of support – 15 March 2017
- CV: Maura Daly

Scientific Coordinating Committee
MRC Unit The Gambia
PO Box 273 Banjul, The Gambia
West Africa
Switchboard (+220) 4495442/6 Ext 2308
Fax (+220) 4495919/4496513
E-mail: scc@mrc.gm
Intranet: http://mrcportal/Committees/SCC/SitePages/Home.aspx
Webpage:https://mrcportal.mrc.gm/Committees/SCC/SitePages/Home.aspx

EFSTH

Edward Francis Small Teaching Hospital

THE REPUBLIC OF THE GAMBIA

15th March, 2017

DEPARTMENT OF PAEDIATRICS

Dr Elio Quesada-Gonzalez
Consultant Paediatrician
Head of Paediatric Department
Edward Francis Small Teaching Hospital
Banjul
The Gambia
Tel: 2637241 / 303818
elioquesadagonzalez@yahoo.com

TO WHOM IT MAY CONCERN

Re: Maura Daly

Public Health for Development MsC candidate, London School of Hygiene and Tropical Medicine, UK

I am in support of the above named student undertaking a research project at the Paediatric Department of EFSTH from 26th June to 4th august 2017.This project will be looking at the acceptability of kangaroo mother care to female relatives of mothers admitted to the neonatal unit at EFSTH and is part of a larger MRC/LSHTM research project into kangaroo mother care.

The student will be supervised by Dr Helen Brotherton, MRC/ LSHTM, and will receive the full support from the Department.

Dr Elio Quesada-Gonzalez
Head of Paediatrics

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Helen Brotherton
LSHTM

26 February 2018

Dear Helen

Study Title: A randomised controlled trial of early continuous skin-to-skin contact versus standard care on survival of hospitalised unstable neonates <2000g in The Gambia

LSHTM Ethics Ref: 14545

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
Other	Charter_DSMB_V1.0_141017	14/10/2017	1.0
Investigator CV	Lawn NIH Biosketch_revMay2017	23/10/2017	1.0
Investigator CV	Short CV AnnaRoca Oct 2017 v2	23/10/2017	1.0
Investigator CV	CV HB June 2017_signed	23/10/2017	1.0
Other	HB GCP certificate March 2017	23/10/2017	1.0
Other	Anna Roca GCP Certificate	23/10/2017	1.0
Information Sheet	ICD neo_V1.0_271017	27/10/2017	1.0
Information Sheet	ICD mat_cg_V1.0_271017	27/10/2017	1.0
Local Approval	MOH Approval Letter_eKMC	30/10/2017	1.0
Protocol / Proposal	eKMC_clinical trial protocol_V1.0_301017	30/10/2017	1.0
Sponsor Letter	Sponsors letter_eKMC_V1.0 301017	30/10/2017	1.0
Covering Letter	Cover letter detailing clarifications 13.02.18	13/02/2018	1.1
Protocol / Proposal	clinical trial protocol_V1.1_13.02.18	13/02/2018	1.1
Information Sheet	ICD neo_V1.1_13.02.18_tracked	13/02/2018	1.1
Information Sheet	ICD mat_cg_V1.1_13.02.2018_tracked	13/02/2018	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,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

C/o MRC Unit: The Gambia @ LSHTM, Fajara
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Email: ethics@mrc.gm

The Gambia Government/MRC Joint

ETHICS COMMITTEE

19 March 2018

Dr Helen Brotherton
MRCG at LSHTM
Fajara

Dear Dr Brotherton

SCC 1591v1.1, A randomised controlled trial of early continuous skin-to-skin contact versus standard care on survival of hospitalised unstable neonates <2000g in The Gambia

Thank you for submitting your proposal dated 14 February 2018 for consideration by The Gambia Government/MRC Joint Ethics Committee at its meeting held on 9 March 2018.

We are pleased to approve your request. With respect to the version number of the ICD, you are advised to submit a letter to the Secretariat clarifying the discrepancy about the version number.

With best wishes

Yours sincerely

Mr Malamin Sonko
Chairman, Gambia Government/MRC Joint Ethics Committee

Documents submitted for review:

- Response Letter – 14 February 2018
- SCC Approval letter – 16 February 2018
- SCC Application Form, version 1.1 – 14 February 2018
- Protocol, version 1.2 – 14 February 2018
- ICD (mat), version 1.1 – 22 January 2018
- ICD (veo), version 1.1 – 22 January 2018
- MOH approval letter – 25 October 2017

REPUBLIC OF THE GAMBIA

MINISTRY OF HEALTH & SOCIAL WELFARE
THE QUADRANGLE
BANJUL

25th October 2017

REF: DHS/HOS/2017/01[05]

Dr. Hellen Brotherton
MRC Unit
FAJARA, The Gambia

RE: A RANDOMISED CONTROLLED TRIAL OF EARLY KANGAROO MOTHER CARE VS STANDARD CARE ON DEATH & NEAR DEATH IN HOSPITALISED UNSTABLE NEONATES <2000g IN THE GAMBIA

I acknowledge receipt of your letter with the above caption dated 4th October 2017 and wish to convey approval for the implementation of the above study at Edward Francis Small Teaching Hospital (EFSTH). The Ministry is keen on this study and would support its implementation.

Please share the study protocol with the EFSTH Chief Medical Director where the study site located. By a copy of this letter the Chief Medical Director EFSTH is duly inform of the study.

Thank you.

VICES

CC Chief Medical Director EFSTH
Program Manager - RCH Unit
File

Tel: 4222117/4227301 Fax: 4229325

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Our ref: QA1078

Dr Helen Brotherton
LSHTM

30th October 2017

Dear Dr Brotherton,

Re: A randomised controlled trial of early continuous skin-to-skin contact versus standard care on survival of hospitalised unstable neonates <2000g in The Gambia

As the authorised representative for the London School of Hygiene & Tropical Medicine (LSHTM), I can confirm that LSHTM will act as the identified Research Sponsor, the organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial, for the above titled project. I can confirm that the research proposal has been reviewed, assessed and registered by the Research Governance and Integrity Office.

It is the Chief Investigator's responsibility to ensure that members of the research team comply with all local regulations applicable to the performance of the project, including, but not limited to: the Declaration of Helsinki (2008), ICH Good Clinical Practice Guidelines (1996), and for projects conducted in the UK: the Medicines for Human Use (Clinical Trials) Regulations (2004), the Research Governance Framework for Health and Social Care (2005), the Data Protection Act (1998) and the Human Tissue Act (2004).

LSHTM carries Clinical Trial/Non Negligent Harm Insurance and Medical Malpractice Insurance applicable to this study. I can confirm that this study does not fall under any exclusion criteria in the policy:

Insurer	Newline
Certification No.	FI0816117 (renewable annually in June)
Finance Cover	£10 million pounds sterling
No. of Participants	346

The Non-Negligent harm policy is worldwide, with the exception of the United States and Canada. The policy is subject to terms, conditions and exceptions.

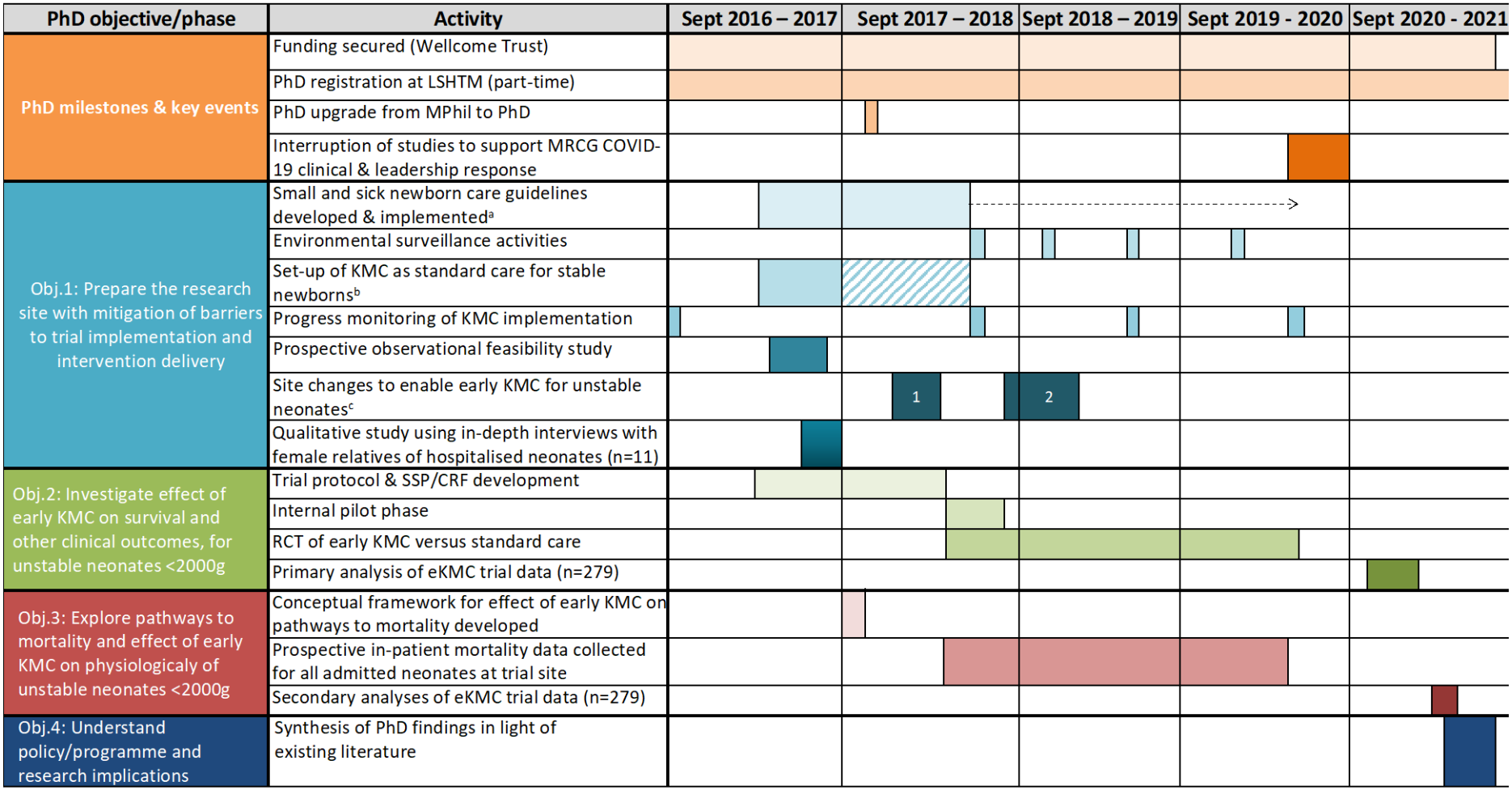
LSHTM Sponsorship is conditional on the project receiving applicable ethical and regulatory approval, complying with LSHTM policies and procedures, as well as successful contract and agreement negotiations from the Research Operations Office, where relevant, before the study commences.

A copy of the ethics and regulatory approval letters **must** be sent to the Quality & Governance Manager prior to the study commencing. Sponsorship is dependent on obtaining local approval for all sites where the research is being conducted. It is recommended that all members of the study team attend Good Clinical Practice (GCP) training every two years.

Yours sincerely,

Patricia Henley
Quality & Governance Manager
T: 020 7927 2626
E: patricia.henley@lshtm.ac.uk

A.2. PhD timeline with key milestones according to PhD objectives



A-3. Environmental surveillance results at eKMC trial site (May 2018 – December 2019)

Date	Isolate	Source
May 2018	*B cepacia*	10% potassium chloride vial (opened)
	B cepacia	Normal saline (opened)
	Pseudomonas spp	Ringers lactate (opened)
	Pseudomonas spp	Liquid soap
	Pseudomonas spp	Oxygen concentrator water container
	Pseudomonas spp	CPAP water container
	Coliform	Sink (neonatal unit high dependency ward)
	Coliform (ESBL)	Suction machine
	Coliform	Ward round trolley
	Coliform	Equipment cabinet
	Klebsiella spp	Suction machine
	Klebsiella spp (ESBL)	Face mask cleaning container
	Klebsiella spp (ESBL)	Sink (KMC unit)
	Klebsiella spp (ESBL)	Water container for visitor hand washing
Oct 2018	*Klebsiella spp*	Equipment cabinet
	Klebsiella spp	Suction machine
	Klebsiella spp	Sink (staff toilet)
May 2019	*Enterobacter (ESBL)*	Suction machine
	Enterobacter	Sink (staff toilet)
	B cepacia	CPAP water container
	B cepacia	Oxygen concentrator water container
	B cepacia	Water container for visitor hand washing
	Pseudomonas spp.	Sink (neonatal unit high dependency ward)
	Pseudomonas spp.	Sink (eKMC trial area)
	Pseudomonas spp.	Sink (staff toilet)
	Raoultella terrigena (ESBL)	IV ceftriaxone vial
Dec 2019	*Klebsiella pnuemoniae (ESBL)*	Sink (staff toilet)
	Klebsiella pneumoniae (ESBL)	Sink (KMC unit)
	B cepacia	Oxygen concentrator water container
	Acinetobacter radioresistens	Sink (neonatal unit high dependency ward)
	Acinebacter iwoffii	CPAP water container
	Raoultella ornithinolytica	Water container for visitor hand washing
	Raoultella ornithinolytica (ESBL)	Suction machine

Infection prevention control actions taken by trial site in response to eKMC surveillance results

June 2018
- Introduction of intravenous fluid checklist & provision of disposable syringes needles with linked HCW training
- Replacement of suction machine & water / cleaning containers
- Changes to methods of cleaning re-usable materials & equipment
- Provision of additional cleaning materials to Neonatal & KMC units
- Daily cleaning of surfaces and sinks with bleach
- Discussion with hospital administrators re. access to running water

Nov 2018
- Continuation of IPC practices with focus on aseptic fluid administration, safe storage of prepared fluids/antibiotics and cleaning of environment, equipment & consumables
- Continuation of advocacy for consistent access to running water for NNU (new tank and water pump installed Jan 2019 with resultant running water supply thereafter)

June 2019
- Running water consistently available on neonatal unit
- Replacement of contaminated buckets
- Continuation of cleaning as schedule as previous

Supplementary file I: Interview Guide

Female Family Kangaroo
In-Depth Interview Guide

Outline :

I. Introduction
II. Warm-up questions
III. Newborn Knowledge
IV. Low Birthweight and preterm knowledge
V. Kangaroo care knowledge

I. Introduction:

Thank you for agreeing to take part in this interview. My name is ..... I am now going to ask you some questions regarding your experiences with caring for newborns, small babies or babies born too early and kangaroo care. As explained, you are free to stop the interview at any time. This interview will be audio-recorded (tape recorded) and will take approximately 40 minutes to an hour. Again, I just want to emphasize that we just want to know about your experiences and thoughts. There are no right or wrong answers; we just want to hear what you think. Thank you for your time.

II. Warm-up questions / Background

Tell me a little bit about yourself. Where were you born? Do you have any children? [Just build up a rapport]
Background:

- Are you married / divorced / widowed / never married?
- Did you finish high school? Did you complete more education after high school?
- What is your religion?
- Do you work? What is your occupation?
- Who do you live with?
- How many children do you have?
- Who helps you to take care of your children?
- Do you have a family member that has had a small or born too early baby?

III. Newborn knowledge

What are the usual ways to care for a newborn?

- Probes: Talk about their experience with newborns, with their own and others.

What does newborn care mean to you?

- Probes: Explore following aspects of newborn care

- When should a baby be bathed? By whom?
- How do you care for the cord? What should be put on it and by whom?
- How do you keep a baby warm, should the baby be wrapped?
- What are the reasons a baby can become sick?
- Who usually helps a newborn mother care for her baby?
- Who should a mother trust to take care of her children when she is not at home?

What are things you can do to make the baby healthy?

Who usually gives new mothers and fathers advice about caring for a baby? Who gives you advice?

What does a good mother do when caring for a newborn?

Has the way you care for newborns changed over time?

- Probes: Did your grandmother or mother do things differently?

What are the typical ways to care for a new mother?

- Probes: Who usually accompanies and supports her? Who gives her advice?
- When a mother and new baby leave the hospital, which house or compound do they go to?

IV. **Experience and perceptions of low birthweight or preterm newborns**

Now I want to know about your experience with small babies or babies born too early

Tell me about the baby you are related to that is in the neonatal unit, why is the baby here?

How do you feel about the baby being in the neonatal unit?

How often have you been here since the baby was admitted?

Do you think being here is helpful to the baby and mother?

Who do you think should come to support the mother and baby?

Why do you think babies are born too early or small?

When a woman has a small baby, or baby born too early in the hospital, who usually comes to support her?

Have you ever had a small baby or baby born too early or cared for one?

- **Probes:**
  - If yes: how did you care for the baby?
  - Did you do things differently than for a normal newborn? If so, what?

- Did you have any trouble caring for the baby? How is it different from normal care? If no; how would you care for the baby?

Would you care differently for twins ?
What are the usual ways to take care of a small bay or babies born too early in your community?

- Probe: Tell me more about this

Are there special ways of caring for small babies? Bathing, feeding?

What is the typical advice a mother of a small baby is given?

How do you know if a baby is too small for normal care?

What are the things mothers or carers have to be most careful about when caring for small babies or babies born too early?

What does the community or neighbours think about small babies or babies born too early? What do other mothers think?

- Probe: Why are they born early? When is too early to survive?

V. Kangaroo Care

Have you heard about or seen kangaroo care?

- Probe: If yes, what is it and where did you first hear about it?
  If no, provide the information sheet and explain concept, check understanding before continuing

Why do you think kangaroo care is done?

Is kangaroo care different from what your mothers or grandmother did with babies born early or small?

What effects do you think kangaroo care has on the baby?

- Probe: is it good or bad?

Why do you think the baby is help in this position?

What effects do you think kangaroo care has on the mother?

If you had a small baby would you choose to do kangaroo care?

- Probe: Why / why not

Do you think kangaroo care is easy or hard?

- Probe: Why and for whom

Are there reasons why it shouldn't / couldn't be done?

How do you think the baby feels, receiving kangaroo care?

How do you think the mother will feel?

Is kangaroo care similar or different to the ways your mother or grandmother would have cared for a small baby?

Do you think it is possible to give kangaroo care for 18 – 20 hours per day?

What are the things mothers or families have to be most careful about when doing kangaroo care?

How do you think the rest of the family feels about kangaroo care?

Is it something the mother will be able to continue at home?

What will be the challenges she will face when doing kangaroo care at home?

How do you feel when you think about kangaroo care?

How would you feel if you were asked to help the mother give kangaroo care to her small baby?

- Probe: Is it different than the normal help you would provide? Easier ? Harder?

Kangaroo care should be given for 18-20 hours a day. Sometimes the mother is tired or recovering from a C-section, or there are twins. If you were asked, how would you feel about providing some of the kangaroo care ?

- Probe: Would you say yes or no?
  If yes, how long would you do it?
  How long do you think the mother would react? The baby?
  Would you do it more than once? If not, why not?
  What circumstances would you do kangaroo care?
  Do you think this is good for the baby ? The mother?

When is the best time for family members to provide kangaroo care?

How often should the family member provide kangaroo care?

Should the father of the baby also provide kangaroo care?

Would your relationship with your family change [if you did kangaroo care] ?

- Probe: If yes, how?

Who besides the mother should or can provide the skin to skin part of kangaroo care?

Who besides the mother or father can provide consent for the baby to receive kangaroo care?

What do you think other mothers will think when they see kangaroo care?

How do you think your community / neighbours will feel about kangaroo care?

Thinking now about all the things we have talked about, is there anything else we haven't discussed that you think is important about kangaroo care?

Thank you so much for taking the time to talk to me. Do you have any questions you would like to ask me?

To Interviewer: Stop recording. Interview ends.

Supplementary file II – KMC information sheet

Kangaroo Mother Care

- Kangaroo mother care is a special way of caring for small or preterm babies
- It is used instead of putting the baby in an incubator or cot
- The baby is kept close to the mothers skin for upto 20 hours / day
- The baby wears a hat and a nappy but otherwise is naked
- A wrapper or pouch is used to keep the baby secure

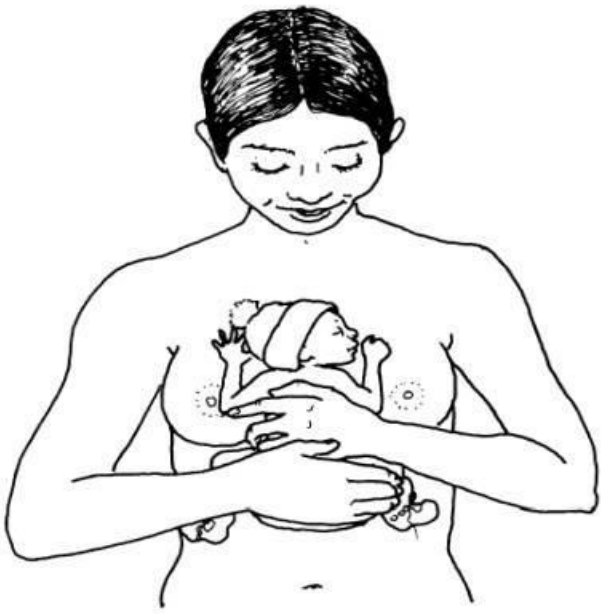


Figure 1: Positioning of the baby during kangaroo care. *WHO*

Figure 2. Mother doing KMC with their small newborn. Taken with consent

- The baby can still breast-feed whilst in the kangaroo position or may require feeding through a tube into the nose or by cup
- Whilst the baby is in position the mother can move around and do activities and can sleep with the baby in kangaroo position
- When the mother needs to shower or use the toilet the baby is put in a warm cot or incubator
- Kangaroo care is started in hospital but can be continued at home following discharge
- The mother is taught about kangaroo more care before starting it and is supported by health care staff during hospital admission

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

Page/line no(s).

Title and abstract

Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2

Introduction

Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	3 - 4
Purpose or research question - Purpose of the study and specific objectives or questions	4

Methods

Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	5
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	7 - 8
Context - Setting/site and salient contextual factors; rationale**	6 - 7
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	6 - 7
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	8
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	7 - 8

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	7
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	9-10
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	8 - 9
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	9
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	7

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	10 - 20
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	10 - 20

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	20 - 23
Limitations - Trustworthiness and limitations of findings	23 - 24

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	24
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	25

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388

ADAPTED SCRIP SCORE FOR MEASUREMENT OF CARDIO-RESPIRATORY STABILITY OUTCOME

		2 points	**1 point**	**0 points**
A	**Cardiovascular stability**: Heart rate (beats per minute)	120 – 160 for 10 mins continuously	100 - 120 or 161 – 200 for >5 out of 10 mins	<100 or >200 continuously for >5 out of 10 mins
B	**Respiratory stability:** Breathing pattern and respiratory rate (RR) (breaths per minute)	Regular breathing And/or RR 20 – 60 continuously for 10 mins	Irregular or periodic breathing with 1 or more pauses for <10 secs And / or RR 20 – 29 or 61 – 100 for >5 out of 10 mins	Irregular breathing with 1 or more pauses for >10 secs And / or Irregular breathing with 1 or more pauses for <10 seconds but which result in oxygen saturation <88% Need for bag-valve-mask ventilation And / or RR <20 or >100 for >5 out of 10 mins
C	**Oxygen saturation (%)**	>88% continuously in room air for 10 mins	>88% continuously for >5 out of 10 mins in oxygen	<88% continuously for >5 out of 10 mins despite oxygen

Stable = 6

Mild – moderately unstable = 3 – 5

Severely unstable = 0 - 2

*Extracted from eKMC trial protocol V4.0 – 18th March 2019

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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
Protocol version	3	Date and version identifier	24
Funding	4	Sources and types of financial, material, and other support	5, 25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 26
	5b	Name and contact information for the trial sponsor	25
	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	25
	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)	26, 27

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
Objectives	7	Specific objectives or hypotheses	7
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	8,9
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	13, 14, 15, 16
	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)	14, 15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16, 17, 19
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
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	17, 18
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)	9, 10

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	20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	20
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	12, 13
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	12, 13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Na
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, 17,18, 19
	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

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	19
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	20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20
	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)	21
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	22, 28
	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	22
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	27
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)	27

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
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	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
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	26
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	26
	31b	Authorship eligibility guidelines and any intended use of professional writers	27
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	26
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not included
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	19

*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.

Statistical Analysis Plan

1. Administrative information

1.1. Title, registration, versions and revisions

Full title:	Protocol for a randomised trial of early kangaroo mother care compared to standard care on survival of pre-stabilised preterm neonates in The Gambia
Acronym:	Early Kangaroo Mother Care (eKMC)
Local reference:	SCC 1591
ClinTrialsGov code:	ClinicalTrials.gov NCT03555981
Trial protocol version:	4.0 (18th March 2019)
SAP Version:	1.1 (24th June 2020)
SAP revision history:	not applicable
Revision history:	None

1.2. Roles & responsibilities:

Principal investigator: Dr Helen Brotherton[1]
Author: Dr Helen Brotherton[1]
Statistician: Abdul Muhammad
Dr Helen Brotherton
Contributors & roles: Professor Simon Cousens[1]: Senior statistician
Prof Anna Roca[2]: contributed to the design of SAP
Diana Elbourne[1]: contributed to the design of SAP
Joy Lawn[1]: contributed to design of SAP
Affiliations: 1. Faculty of Epidemiology and Population Health, and MARCH Centre, London School of Hygiene & Tropical Medicine (LSHTM), Keppel Street. London, UK
2.MRC Unit The Gambia at LSHTM, Atlantic Road, Fajara, The Gambia

1.3. Signatures:

Statistician: Name: **Abdul Khalie Muhammad**

Signature: _____

Date: **24th June 2020**

Senior statistician: Name: ___**Simon Cousens**_____

Signature: _ ____

Date: **24th June 2020**

PI: Name: Helen Brotherton

Date: 26th June 2020

2. Introduction

2.1. Background / rationale

Neonatal mortality remains unacceptably high and complications of prematurity are the most common, direct, cause of death in children aged under 5y. Nearly half of all preterm neonates die within the first 24h after birth, before post-natal stabilisation has occurred. Focusing on improving hospital care for preterm neonates in the early neonatal period is a global research and public health priority if global neonatal mortality reduction targets are to be met.

Kangaroo mother care (KMC) is recommended as standard care for all hospitalised babies <2000g who are fully stable and have completed the post-natal stabilisation process. It was developed in Colombia in 1978 and has since been adopted in both high-income (HIC) and low-middle income countries (LMIC) as an adjunct to incubator care. KMC is a package of care with the key component being prolonged, continuous skin-to-skin contact between the nearly naked baby and mother/caregiver. This leads to promotion of early and exclusive breastfeeding and early discharge from hospital. There is strong evidence of mortality (36 – 51% reduction) and clinical benefits (reduced nosocomial infection, improved growth, and stability) for KMC in stabilised preterm neonates. However, there is an evidence gap for KMC in neonates who have not completed stabilisation and this is a potentially feasible, game changing intervention for health facility care of the small and sick neonate. There is also an evidence gap with respect to our understanding of how KMC reduces nosocomial and severe infections.

2.2. Hypothesis

Using early continuous skin-to-skin contact in pre-stabilised preterm neonates will improve survival by:

1. Early onset, early impact, stabilisation pathways which improve thermal control and promote cardio-respiratory stabilisation
2. Early onset, late impact causal pathways, including prevention of late-onset infections, gastro-intestinal stability and prevention of apnoea of prematurity.

2.3 Objectives

Objective 1. To assess the effect of early continuous skin-to-skin contact on survival of pre-stabilised preterm neonates <2000g

Objective 2. To assess the effect of early continuous skin-to-skin contact on other important clinical outcomes (growth, late onset infection and duration of hospital stay) for pre-stabilised neonates <2000g

Objective 3. To assess the safety of providing early continuous skin-to-skin contact to pre-stabilised neonates <2000g

Objective 4. To explore early and late mechanistic pathways for the beneficial effects of early continuous skin-to-skin contact compared to standard care in pre-stabilised neonates <2000g

3. Study methods

3.1. Trial design

This individually randomised, controlled, superiority trial compared 2 parallel groups of hospitalised, pre-stabilised neonates <2000g receiving either early continuous skin-to-skin contact (KMC started at <24h since admission) (intervention group) or standard care (KMC started at >24h since admission and once stable) (control group) (ratio 1:1). The intervention was un-blinded to participants and researchers. Primary outcome was all-cause mortality at 28d. The trial was conducted at the neonatal unit of the national teaching hospital (Edward Francis Small Teaching Hospital) in The Gambia from May 2018 to April 2020.

3.1.1. Eligibility criteria

Inclusion criteria:

- New admission to the neonatal unit at EFSTH during the study period
- Admission weight less than 2000g
- Age 1 – 24h at time screening begins
- Alive at time of enrolment
- Singleton or completed twin birth admission
- Written informed consent provided by a parent/caregiver willing to provide the intervention

Exclusion criteria:

- Congenital malformation which is incompatible with life or requires immediate surgical correction
- Severe jaundice needing immediate management
- Seizures
- Clinically stable as assessed over a pre-defined period of cardio-respiratory monitoring
- Severely unstable as assessed over a pre-defined period of cardio-respiratory monitoring
- Completed triplet admission
- Mother and/or neonate already enrolled into another MRCG study at time of hospital admission

- No study bed available

3.1.2. Intervention procedures

Participants in the intervention arm commenced the continuous skin-to-skin contact aspect of KMC within 24h after admission, aiming for >18h/day. It was provided by the first available caregiver (mother, father or other relative) in the trial area of the study site at the same time as any other medical or nursing care required by the neonate (E.g. oxygen, intravenous fluids, antibiotics, gastric feeds). Clear stopping criteria were in place for when to stop KMC due to clinical reasons. Skin-to-skin contact was re-commenced when stability criteria were met, as per the control arm.

3.1.3. Control procedures

Participants were managed in an incubator or under a radiant heater, naked except for a woollen hat and nappy or wrapped in a cloth. The parent/caregiver could touch, hold, and feed the neonate as per standard practice but KMC was not provided until stability criteria were met and at greater than 24h since hospital admission. Participants received intermittent KMC in the trial area and continuous KMC was started after transfer to the adjacent KMC unit.

3.1.4. Procedures for both arms

A pragmatic study design was used with a standardised preterm/LBW clinical management protocol based on current standard care. All management was provided by study site staff in collaboration with research clinicians with compliance to the management protocol monitored daily.

3.2 Randomisation & allocation

An independent statistician generated a randomisation sequence using VBA (Visual Basic Application) within an Access database to produce two random number tables with stratification by admission weight categories (<1200g; ≥1200g). Random permuted blocks of varying sizes were used with 1:1 allocation. Allocation concealment was performed with sequentially numbered, opaque, sealed envelopes prepared by an independent researcher and accessible to study team only. Following collection of baseline data, the study nurse opened the next numbered envelope for the correct weight category. The participant identifier, date and time were recorded on the outside of the envelope prior to opening, to identify any subversion of allocation sequence. Twins were allocated to the same arm, according to the first eligible twin's weight.

3.3 Sample size

A total of 392 participants (1:1 ratio) were required to detect a 30% relative reduction in the primary outcome (power 80%, alpha=0.05). This is based on an expected mortality rate of 48%, which was adjusted from observed rates of 56% to account for 15% mortality reduction due to trial implementation. Loss to follow up rates were low (<2%) due to the restricted geographical area, co-ordination of follow-up with routine appointments and re-imbursement of travel expenses.

3.4 Statistical interim analyses and stopping guidance

An un-blinded interim analysis was conducted by the DSMB in December 2019, once 50% of the intended sample size (n=196) were recruited and followed-up. The interim analysis included consideration of primary and secondary outcomes with the exception of intestinal carriage of ESBL-producing K*lebsiella pneumoniae*. Stopping rules for efficacy were pre-defined by the DSMB using the Haybittle-Peto rule and there was no adjustment of significance levels following the interim analysis. The DSMB recommended that the trial continue with no protocol changes.

3.5 Timing of final analysis

Data cleaning and data locking were performed once the final participant recruited during the study period completed follow up. All outcomes will be analysed at the same time, with the exception of secondary outcome "Intestinal carriage of ESBL *Klebsiella pneumoniae"* which may be performed at a later date, dependent on funding.

The statistical analysis plan will be added to the study protocol at clinicaltrials.gov before closure of the database and before any analyses are conducted.

3.6 Timing of outcome assessments

Outcomes are assessed according to the following schedule:

Timing	Outcome
24h after study participation	• Cardio-respiratory stability (Mean adjusted SCRIP score) • Hypothermia (Prevalence of participants with temperature <36.5°C)
Daily whilst admitted to neonatal unit Weekly (day 7, 14, 21, 28) whilst admitted to KMC unit Ad-hoc reviews in event of clinical deterioration	• Time from start of study procedures to death (hours) • Incidence of clinically suspected infection from 3 – 28 days of age or latest follow-up
Day of discharge	• Exclusive breastfeeding • Duration of admission
Age 28 +/- 5 days	• Survival status (alive / died) • Weight gain (mean weight gain in g/day from baseline) • Prevalence of participants with intestinal carriage of ESBL-Klebsiella pneumoniae

4. Statistical principles

4.1 Confidence intervals (CIs) & P values

We consider P values <0.05 as statistically significant evidence of a difference between arms for all pre-specified outcomes. Results will be presented with 95% Cis.

4.2 Multiplicity

No adjustments for multiple statistical tests will be made.

4.3 Analysis populations

Analysis of primary and secondary outcomes will be conducted on an intention-to-treat basis for all enrolled participants. A sensitivity analysis will be performed excluding any participants

who were recruited in error and did not meet the eligibility criteria as stated in the most recent trial protocol.

4.4 Adherence and protocol deviations

4.4.1 Adherence to the intervention

Adherence to the intervention was monitored by direct observation of time a participant spent in KMC position and was manually recorded on paper CRFS by trial personnel. The following variables were recorded: date and time of first KMC contact; relationship of person providing KMC to participant; frequency and duration of each KMC session; number of neonates receiving KMC during each session and reason for stopping KMC session. The raw data were manually inputted to Excel and the total daily dose (from start of study procedures) of KMC received was automatically calculated before being reconciled with the trial database for every in-patient day. The average daily dose of in-patient KMC per duration of admission was automatically calculated in REDCap for each participant.

4.4.2 Definition of protocol deviation

A major protocol deviation is defined as a departure from the Trial Protocol or ICH-GCP standards which had an impact on the conduct of the study, the credibility of the data or safety of participants. This includes recruitment of an ineligible neonate, recruitment without consent or use of impartial witnesses; participants in the control arm receiving the intervention inappropriately or any deviation that resulted in a Serious Adverse Event (SAE, see section 6.5). Major deviations were reported to the sponsors and SCC / ethics committees within 5 working days, as per MRCG SOPs.

All other deviations from the study protocol or GCP standards were considered to be minor and were reported to the monitors on a monthly basis and the ethics committees on an annual basis. Only major protocol deviations will be summarised and reported in any publication of trial results.

5. Study population

5.1 Screening data

The total number of neonatal admissions and proportion of those weighing ≤2000g was prospectively recorded and will be presented as part of a separate survival analysis comparing mortality before and during the trial. Clinically eligible neonates who were not recruited will be compared with recruited neonates to compare general characteristics (age at admission, sex, referral status (inborn/outborn), stability at first screening) and outcomes (in-hospital mortality).

5.2 Eligibility

Eligibility was assessed in all neonates with referral weight ≤2000g as soon as possible after admission and once aged >1h old. Weight was confirmed using calibrated SECA™ 757 digital weighing scale and source documents were checked for age and other study involvement. All potentially eligible neonates aged <24h underwent an examination with cardio-respiratory stability assessed over 10-minutes using Nonin™ 2500A pulse oximeter.

Inclusion criteria:

- New admission of singleton or twin
- Weight <2000g as per study scale
- Aged 1 - 24h old when screening begins
- Mother or other caregiver available and willing to provide intervention

Exclusion criteria:

- Triplets who were all admitted to study site
- Congenital malformation not compatible with life or needing immediate surgical intervention
- Severe jaundice
- Seizures
- Stable as assessed during cardio-respiratory screening
- Severely unstable as assessed during cardio-respiratory screening or died during screening
- No study bed available
- Neonates/mothers enrolled in another research study
- No written informed consent from parent or caregiver within 24h of admission

5.3 Recruitment

The number and flow of subjects through screening, randomisation, allocation, follow-up, and analysis will be documented, as per CONSORT 2010 guidelines. Reasons for exclusion, withdrawal and non-analysis will be described (Fig.1).

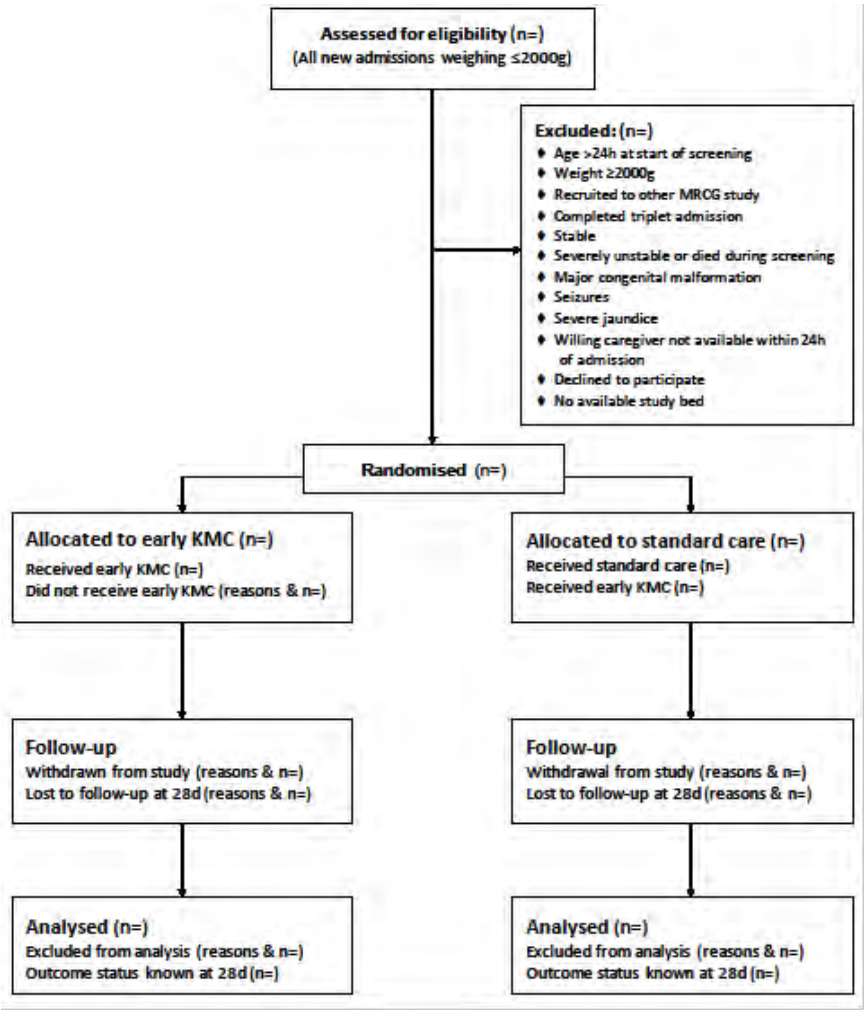


Figure 1. Trial flow diagram, as per CONSORT guidelines 2010

5.4 Withdrawal / follow-up

The number and proportion of participants who permanently withdrew from the study will be described with reasons for withdrawal. The proportion of participants who complete follow-up at 28+/-5 days will be described. Participants who are permanently withdrawn or lost to follow-up will be included in the analysis using data collected up-to the point that they are lost or withdrawn. An exception to this is if a participant withdraws and requests for no data to be used during analysis.

5.5 Baseline patient characteristics

Baseline socio-demographic and clinical characteristics of the neonate, mother and perinatal period will be summarised for each arm by number and proportion (categorical variables) and either means with standard deviations or medians and interquartile ranges, as appropriate (continuous variables). This will include comparison of treatments received prior to enrolment. Statistical tests of differences in baseline characteristics will not be performed.

5.6 Adherence to the Standardised Preterm Management Protocol

Compliance to the standardised preterm/LBW management protocol was monitored daily by the field team and key indicators of standard hospital management were recorded as concomitant medications (E.g. antibiotic therapy, provision of caffeine citrate or aminophylline to prevent apnoea of prematurity). Indicators will be compared between arms from time of study enrolment to discharge or death and will include receipt of key management and investigations. Characteristics will be descriptively summarised with categorical data presented using counts and percentages and continuous data presented using number of patients, mean, median, standard deviation, minimum, maximum and IQR, as appropriate. Data will be presented in the form of a table with arm-specific and total data. Statistical tests comparing concomitant treatments between both arms will be conducted, using Fishers exact tests for categorical variables and two sample *t* test for continuous variables to calculate p values with 95% CIs.

5.7 Adherence to the intervention

A descriptive analysis of KMC provided to both arms will be conducted. The following will be calculated as indicators of adherence and presented in a table format: mean chronological age at first KMC contact; mean time since admission at first KMC contact; mean daily dose of KMC (h/day) for first 7 days since enrolment; mean daily dose of inpatient KMC, per number of days admitted. The proportion of patients transferred from the neonatal unit to the KMC unit for each arm will be described with mean (and standard deviations) chronological ages at admission. Individual patient data on the actual daily dose of in-patient KMC, up-to 28 days of age, will be represented for both control and intervention arms using heat maps and box plots. This will provide a visual representation of the intervention provided over the study period. The number and proportion of participants in the intervention arm who met KMC stopping criteria for clinical reasons will be described with reporting of reasons and mean age at time of stopping.

6. Analysis of outcomes

6.1 Outcome definitions

Primary outcome:
All-cause mortality at 28d

Secondary outcomes:
1. Time from intervention/control procedures starting to death (days & hrs)
2. Mean cardio-respiratory stability at 24h of intervention (aSCRIP score)
3. Prevalence of hypothermia (T<36.5°C) at 24h of intervention
4. Mean daily weight gain (g/day) at 28d
5. Proportion of infants exclusively breastfeeding at discharge
6. Mean duration of hospital admission (days & hours)
7. Incidence of clinically suspected infection after 3 days and by 28 days or latest follow up
8. Prevalence of neonatal intestinal carriage of ESBL-Klebsiella pneumoniae at 28d

6.2 Analysis methods

Primary & secondary outcome analysis

Primary outcome:
The number of subjects who met criteria for the primary outcome will be calculated for each arm and generalised estimating equations used to calculate intervention efficacy. This will be presented as a relative effect (E.g. risk ratio) and absolute effect (risk difference) with a measure of precision (E.g. 95% CI). The results will also be expressed as the number needed to treat for benefit. Kaplan-Meier survival curves will also be used to present the risk ratio and risk differences visually for both arms.

Secondary outcomes:
Analysis of secondary outcomes will be performed according to type of data (mean, proportion, number, incidence) and using either number of subjects or person time as the denominator, as appropriate. Binary variables will be compared between arms using generalised estimating equations. Continuous variables will be compared using random effects models. The appropriate effect size will be presented. Survival analysis of the time to death within first 28 days after birth will be performed using cox regression with frailty to account for twins. Random effects models will be used to account for multiple episodes for the same participant (E.g. infection). A 95% CI will be presented for the treatment effect for all outcomes.

Adjustments for potential confounders / covariates:
The key covariates which are known to independently predict neonatal mortality (primary outcome) are: Admission weight, gestational age, and twin status. Two analyses will be performed for all outcomes:

Primary analysis: Adjustment for covariates (weight category, gestational age, and twin status) will be performed regardless of whether there are differences in baseline covariates between arms. Linear mixed effects models will be used for continuous data. Generalised estimating equations will be used for binary data. Both analyses will be reported but the unadjusted analysis is considered the primary analysis.

Exploratory analysis: No adjustment for covariates

Subgroup analysis

Subgroup analysis for all outcomes will be performed for infants according to: birth weight categories ; singleton or twin status. The relative measures of effect within each of these subgroups will be estimated (with 95% CIs) and a test of interaction performed and reported.

Sensitivity analysis

A sensitivity analysis will be performed excluding any participants recruited in error as per most recent protocol definitions and eligibility criteria.

6.3 Missing data

The amount of missing data is expected to be low (<5%) and a complete case analysis will be conducted.

6.4 Additional analyses

6.4.1. Effect of intervention on cardiorespiratory stability

A detailed analysis of cardio-respiratory stability will be done for the first 24h of study participation. This will include but is not restricted to a descriptive analysis of: average heart rate; average oxygen saturation; proportion of time spent with abnormal heart rate or oxygen saturation over first day of study participation. Differences between arms will be analysed using Fishers exact tests for categorical variables and two sample *t* test for continuous variables to calculate p values with 95% CI. This may be reported with the primary analysis results or as a secondary analysis.

6.5 Harms

Adverse events and SAEs will be listed and defined with reference to standardised criteria where appropriate. The methods used for data collection and attribution of events will be described.

The number and proportion of participants with an SAE (life-threatening event; risk of disability; re-admission to hospital or prolonged hospital stay >28d) will be presented for both arms. Death will not be included as this is the primary outcome of the trial.

A detailed analysis of blood glucose levels over the first 24h of study participation will be performed as a proxy indicator of disturbance to the IV fluid administration. This will involve number and proportion of participants with hypoglycaemia or hyperglycaemia at defined time points as well as mean glucose level at baseline, 12h and 24h. The significance level will be calculated using chi squared or Fisher's exact tests for categorical variables. Continuous variables will be compared using Student's t-test or nonparametric tests, when appropriate. The appropriate effect size will be presented, using risk ratios for binary outcomes and difference between means for continuous data.

6.6 Statistical software

STATA Version 16 will be used for all analyses with the exception of generation of heat maps to report intervention adherence, which will be done in R version 3.6.3.

References:

Gates S, Brocklehurst P. How should randomised trials including multiple pregnancies be analysed? BJOG. 2004 Mar;111(3):213-9.

e-Table 1. Additional baseline characteristics for intention-to-treat population

	Standard care (n=141)	KMC before stabilisation (n=138)
Neonatal		
Admission length (cm) median (IQR)[a]	40·1 (37·3 – 42·3)	40·1 (37·6 – 42·0)
Admission head circumference (cm) median[b] (IQR)	28·5 (26·3 – 29·9)	28·2 (26·8 – 29·5)
NMR2000 score,[c] median (IQR)	17·2 (14·5 – 19·5)	17·6 (14·7 – 19·5)[d]
Hypothermia (axillary temp <36.5°C), N° (%)	54 (38%)	46/137 (34%)
Hyperthermia (axillary temp >37.5 °C), N° (%)	15 (11%)	19/137 (14%)
Hypoglycaemia (<2.6 mmol/L), N° (%)	4 (3%)	8/134 (6%)
Hyperglycaemia (>6.9 mmol/L), N° (%)	19 (13%)	13/134 (10%)
Respiratory rate (bpm), median (IQR)[e]	56·1 (47·8 – 66·7)	57·1 (47 – 65·9)
Heart rate (bpm), median (IQR)[f]	138·3 (130 - 149)	138·4 (125 – 148·3)
Bag valve mask ventilation, N° (%)	1 (1%)	4 (3%)
Chest compressions, N° (%)	3 (2%)	3 (2%)
IV Fluid bolus, N° (%)	9/140 (6%)	5 (4%)
Gastric tube in-situ, N° (%)	85 (60%)	84 (61%)
Expressed breast milk given, N° (%)	3 (2%)	7 (5%)
Blood transfusion, N° (%)	1 (1%)	2 (2%)
Mother		
Maternal age (years) median (IQR)	26 (21 - 31)	25 (20 - 30)
English illiterate, N° (%)	88/140 (63%)	77/137 (56%)
Married, N° (%)	132 (94%)	126 (91%)
Level of education, N° (%)		
No formal education	42/138 (30%)	42/137 (31%)
Islamic school	26/138 (19%)	30/137 (22%)
Primary school	21/138 (15%)	13/137 (9%)
Secondary school	42/138 (30%)	43/137 (32%)
College/university	7/138 (5%)	9/137 (7%)
Employment, N° (%)		
No formal employment[g]	112/139 (81%)	118/137 (86%)
Domestic service	1/139 (1%)	6/137 (4%)
Unskilled manual	7/139 (5%)	3/137 (2%)
Skilled manual	8/139 (5%)	3/137 (2%)
Sales & service or clerical	5/139 (4%)	0/137 (0%)
Professional/managerial/technical	7/139 (5%)	7/137 (5%)
Urban residence, N° (%)	113 (80%)	107/137 (78%)
Parity, N° (%)		
Primiparous	38 (27%)	50/136 (37%)
2 – 7	99 (70%)	78/136 (57%)
>7	4 (3%)	8/136 (6%)
Maternal co-morbidities, N° (%)		
Hypertension	22 (16%)	32 (23%)
Anemia (<10g/dl) during 2nd or 3rd trimester	4 (3%)	5 (4%)
HIV	2 (1%)	2 (1%)
Infection needing antibiotics in 3rd trimester	3 (2%)	1 (1%)
Bleeding needing blood transfusion	3 (2%)	0 (0)
Eclampsia	1 (1%)	1 (1%)
Diabetes	1 (1%)	1 (1%)
Antenatal clinic visits, N° (%)		
No visits	12/140 (9%)	4/136 (3%)
1 visit	18/140 (13%)	19/136 (14%)
2 – 4 visits	87/140 (62%)	83/136 (61%)
5 or more antenatal clinic visits	23/140 (16%)	30/136 (22%)
Tetanus vaccine (at least 1 dose), N° (%)	102 (72%)	112 (81%)

Malaria IPT (at least 1 dose), Nº (%)	126 (89%)	121 (88%)
Perinatal		
Delivery lasted >24h, Nº (%)	28/140 (20%)	30 (22%)
Apgar score at 5 minutes (median)(IQR)[h]	9 (7 - 10)	10 (7 - 10)
Maternal antibiotics within 7 days before birth, Nº (%)	14/140 (10%)	17 (12%)
Any septic risk factor, Nº (%)	50/139 (36%)	40/137 (29%)
PROM >18h	24/139 (17%)	18/137 (13%)
Maternal fever within 48h of delivery	30/139 (22%)	27/137 (20%)
Foul smelling liquor	9/138 (7%)	6/137 (4%)
Chorioamnionitis	0/140 (0)	1/137 (1%)
Cord hygienically cut,[i] Nº (%)	98 (70%)	95 (69%)
Cord hygienically clamped,[j] Nº (%)	133 (94%)	132 (96%)
Bathed after delivery, Nº (%)	1 (1%)	1 (1%)

a) Admission length missing for 7 participants, n = 138 for control arm and n=134 for intervention arm
b) Admission head circumference missing for 4 participants, n=139 for control arm and n=136 for intervention
c) NMR score is a validated mortality risk score including the following parameters: Birthweight; oxygen saturation level and highest level of respiratory support needed (Medvedev MM et al, 2020)
d) NMR score missing for 5 participants in the intervention arm
e) Baseline respiratory rate missing for 5 participants, n=140 for control arm and n=134 for intervention arm
f) Baseline heart rate missing for 6 participants, n=139 for control arm and n=134 for intervention arm
g) Subsistence farming and informal childcare / house-work or informal childcare were classified as being not formally employed
h) Apgar score at 5-minutes missing for 166 participants, n=48 for control arm and n=65 for intervention arm
i) Hygienic cord cutting defined as cutting with clean razor or scalpel
j) Hygienic cord clamping defined as new plastic cord clamp used
Abbreviations: HIV = Human Immunodeficiency Virus; I = Intervention; IPT = Intermittent prophylactic treatment; IQR = Interquartile range; IV = Intravenous; NMR2000 = neonatal mortality risk 2000 score; PROM = Prolonged rupture of membranes.

e-Table 2. Secondary analysis for eKMC primary and secondary outcomes, adjusted for twin status, admission weight and gestational age

	Standard care	KMC before stabilisation	Effect size (95% CI)	P value
All-cause mortality at 28 days, N° (%)	30/133 (23%)	28/136 (21%)	RR= 0·93 (0·63 – 1·36)	0·699
Time to death (h), median (IQR)	N=30 106 (39 – 142)	N=28 92 (68 – 213)	HR= 0·91 (0·54 – 1·53)	0·716
aSCRIP score at 24h of enrolment, median (IQR)	N=133 5 (4 – 6)	N=133 5 (4 – 5)	MD – 0·06 (-0·26 – 0·14)	0·541
Hypothermia (T<36·5 °C) at 24h of enrolment, N° (%)	53/133 (40%)	51/133 (38%)	RR= 0·92 (0·69 – 1·22)	0·574
Exclusive breastfeeding[a] at discharge, N° (%)	105/107 (98%)	107/109 (98%)	RR= 0·99 (0·96 – 1·01)	0·381
Clinically suspected infection from 3 – 28 days, N° (%)	21/135 (16%)	28/136 (21%)	RR= 1·29 (0·79 – 2·12)	0·304
Duration of admission (days), mean (SD)	N=104 386·4 (240·7)	N=107 400·7 (266·8)	MD 7·5 (-49·0 – 64·0)	0·796
Weight gain at 28d (g/day), mean (SD)	N=99 12·6 (12·2)	N=103 10·2 (10·2)	MD -2·3 (-5·2 – 0·63)	0·125

a) Exclusively breastfeeding defined as only receiving breastmilk and no formula milk supplementation
Abbreviations: CI = confidence intervals; HR = Hazard ratio; MD = mean/median difference in intervention arm; RR= risk ratio; SD = standard deviation

e-Table 3. Sensitivity analysis of eKMC outcomes excluding participants not meeting eligibility criteria at start of intervention/control procedures[a]

	Standard care	KMC before stabilisation	Effect size (95% CI)	P value
All-cause mortality at 28 days, N° (%)	28/129 (24%)	28/124 (23%)	RR= 1·04 (0·65 – 1·65)	0·867
Time to death (h), median (IQR)	N=28 98·5 (34 – 128)	N=28 91·5 (68 – 213)	HR= 1·02 (0·61 –1·73)	0·933
aSCRIP score at 24h of enrolment, median (IQR)	N=125 5 (4 – 6)	N=121 5 (4 – 5)	MD -0·1 (-0·32 – 0·09)	0·264
Hypothermia (T<36·5 °C) at 24h of enrolment, N° (%)	49/125 (39%)	46/121 (38%)	RR= 0·97 (0·71 – 1·33)	0·849
Exclusive breastfeeding at discharge,[b] N° (%)	99/101 (98%)	94/96 (98%)	RR= 1·0 (0·96 – 1·04)	0·978
Clinically suspected infection from 3 – 28 days, N° (%)	20/129 (16%)	28/124 (23%)	RR= 1·46 (0·87 – 2·45)	0·156
Duration of admission (days), mean (SD)	N=100 16·2 (10·2)	N=95 17·0 (11·4)	MD 0·5 (-61·5 – 83·5)	0·767
Weight gain at 28d (g/day), mean (SD)	N=97 12·2 (11·8)	N=92 10·3 (10·3)	MD= -1·9 (-5·0 – 1·28)	0·244

a) Total of 24 neonates were excluded from this analysis. Two neonates were recruited in error: One aged >24h and one who was incorrectly classified as being moderately unstable during screening but was severely unstable. 22 neonates were excluded who met stability criteria at time of screening but either improved or deteriorated prior to baseline data collection and start of intervention/control procedures (stable=16; severely unstable =6).
b) Exclusively breastfeeding defined as only receiving breastmilk and no formula milk supplementation
Abbreviations: CI = confidence intervals; HR = Hazard ratio; MD = mean/median difference in intervention arm; RR= risk ratio; SD = Standard deviation.

e-Table 4. Overview of neonates with blood-culture confirmed infections from 3d – 28d, including outcome and phenotypic MDR status of bacterial isolates

Sex	Age at illness onset (days)	Gest. age (weeks)	Adm. weight (g)	Isolate (MDR)[a]	Antibiotic susceptibility (S/R)			Outcome
					3rd gen ceph	Gent	Cipro	
Intervention arm								
Female	3.2	34	1730	*Burkholderia cepacia*	S	R	R	Recovered
Male	4.7	36	1634	*Burkholderia cepacia*	S	R	R	Recovered
Male	3.5	32	1606	*Shigella spp*. (MDR)	R	R	R	Died
Female	3.8	29	1032	*Acinetobacter spp*. (MDR)	R	R	R	Died
Female	12.9	28	1500	*Klebsiella pneumoniae*[b] (MDR)	R	S	R	Died
				Enterobacter spp[b] (MDR)	R	R	R	
Male	5.6	32	1544	*Shigella spp*. (MDR)	R	R	S	Recovered
Control arm								
Female	4.8	32	1366	*Shigella spp*. (MDR)	R	R	R	Died
Male	4.6	30	1468	*Pseudomonas spp*. (MDR)	R	R	R	Died
Male	11.7	32	1202	*Pseudomonas spp*.	R	S	S	Died
Male	8.1	34	1434	*Raoultella Ornithinolytica* (MDR)	R	R	R	Died

a) Phenotypic MDR defined as resistance to at least one agent in ≥3 different classes of antimicrobial agents with resistance determined as per CLSI 2018 guidelines
b) Mixed growth from one participant
Abbreviations: MDR = multi-drug resistant; R = Resistant; S = sensitive; SD = standard deviation; spp = species

e-Table 5. Non-fatal Serious Adverse Events (SAE) during eKMC trial for intention-to-treat population

Non-fatal SAE type[a]	Standard care N=141	KMC before stabilisation N=138	Total N=279
Life threatening,[b] Nº (%)	11 (8%)	13 (9%)	24 (9%)
Risk of disability,[c] Nº (%)	7 (5%)	6 (4%)	13 (5%)
Prolonged hospitalisation >28 days, Nº (%)	5 (4%)	7 (5%)	12 (4%)
Hospital re-admission within 28 days, Nº (%)	5 (4%)	4 (3%)	9 (3%)
Total non-fatal SAEs / study population, Nº (%)	28 (20%)	30 (22%)	58 (21%)

a) Classified according to final SAE report for all participants.
b) Life threatening SAEs defined as apnoea needing resuscitation, severe instability as per protocol definition or any other life threatening situation as assessed by a clinician.
c) Defined as any condition placing the participant at increased risk of permanent or temporary disability, such as suspected or confirmed meningitis, jaundice needing treatment or acquired hydrocephalus requiring medical or surgical intervention.
Abbreviations: KMC = Kangaroo mother care; SAE = Serious adverse event

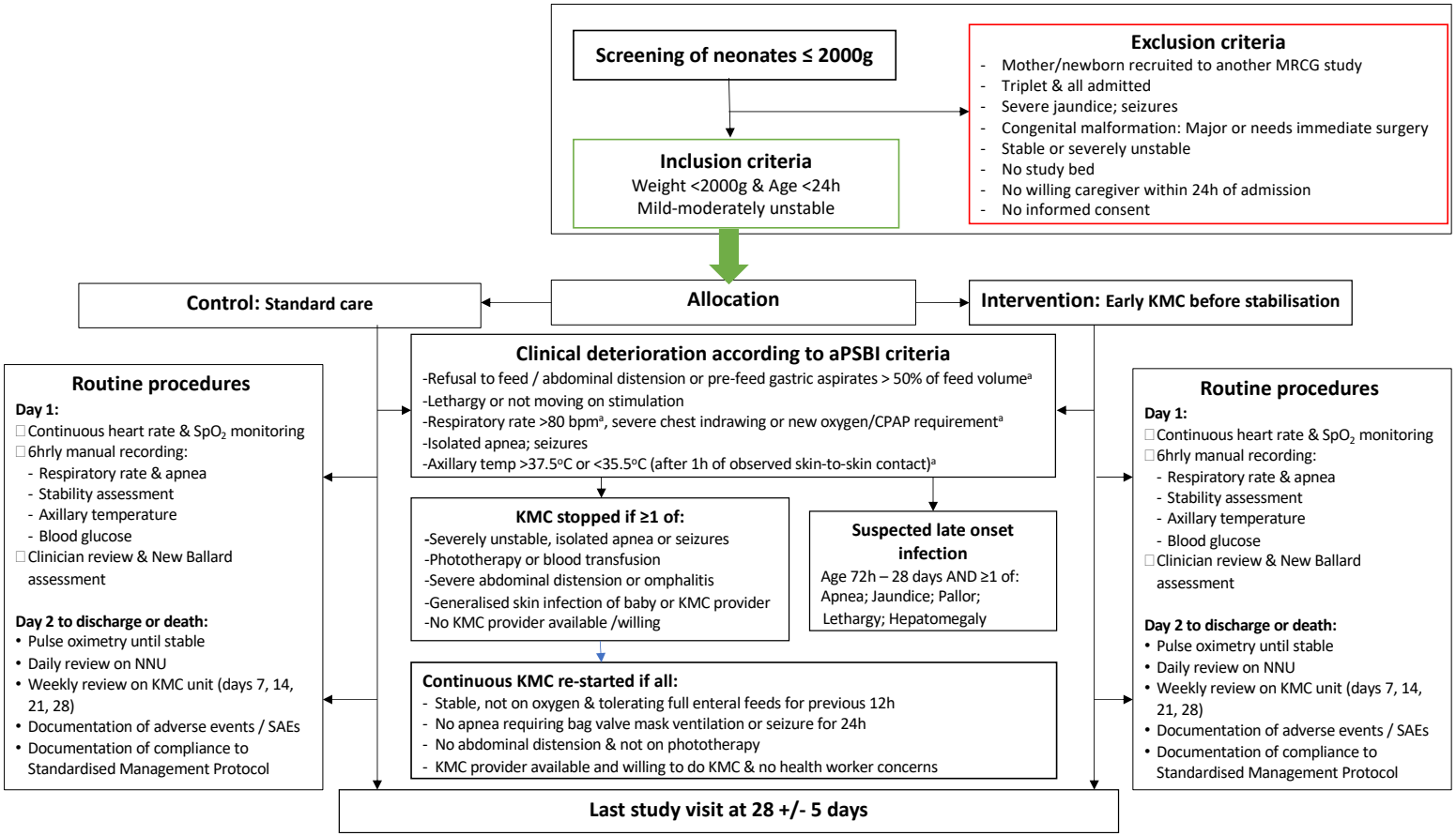
e-Table 6. Concomitant treatments received by intention-to-treat eKMC trial population during hospitalisation

	Standard care (n=141)	KMC before stabilisation (n=138)	P value[a] (95% CI)
Oxygen, Nº (%)	137 (97%)	131 (95%)	0·337 (-0·20 – 0·07)
bCPAP, Nº (%)	18 (13%)	20 (14%)	0·674 (-0·10 – 0·06)
≥1 episode of bag-valve-mask ventilation, Nº (%)	36 (26%)	32 (23%)	0·649 (-0·08 – 0·12)
≥1 episode of chest compressions, Nº (%)	30 (21%)	29 (21%)	0·957 (-0·09 – 0·10)
Gastric tube feeding, Nº (%)	121 (86%)	126 (91%)	0·103 (-0·13 – 0·01)
Maintenance IV fluids, Nº (%)	128 (91%)	126 (91%)	0·878 (-0·07 – 0·06)
≥1 10% Dextrose bolus (IV) for hypoglycaemia, Nº (%)	50/136 (37%)	56/135 (41%)	0·426 (-0·16 – 0·07)
Mothers' expressed breast milk, Nº (%)	124 (88%)	124 (90%)	0·611 (-0·09 – 0·05)
Formula milk, Nº (%)	24 (17%)	28 (20%)	0·483 (-0·12 – 0·06)
Phototherapy, Nº (%)	8 (6%)	9 (7%)	0·767 (-0·06 – 0·05)
Blood transfusion, Nº (%)	11 (8%)	10 (7%)	0·874 (-0·06 – 0·07)
IV Ampicillin, Nº (%)	140 (99%)	137 (99%)	0·988 (-0·02 – 0·02)
Number of ampicillin doses, mean (SD)	8.4 (4.2)	9.7 (7.9)	0·076 (-2·80 – 0·14)
IV Gentamicin, Nº (%)	140 (99%)	137 (99%)	0·988 (-0·02 – 0·02)
Number of gentamicin doses, mean (SD)	4.8 (2.8)	5.3 (3.2)	0·208 (-1·16 – 0·25)
IV Ceftriaxone, Nº (%)	33 (24%)	30 (22%)	0·715 (-0·08 – 0·12)
Number of ceftriaxone doses, mean (SD)	5.6 (4.0)	5.7 (4.1)	0·904 (-2·16 – 1·92)
IV Flucloxacillin, Nº (%)	6 (4%)	6 (4%)	0·970 (-0·05 – 0·05)
IV Ciprofloxacin, Nº (%)	2 (1%)	4 (3%)	0·394 (-0·05 – 0·02)
IV Metronidazole, Nº (%)	11(8%)	7/137 (5%)	0·362 (-0·03 – 0·08)
IV Meropenem, Nº (%)	4 (3%)	0 (0)	0·046 (0·001 – 0·06)
IV Co-amoxiclav, Nº (%)	11 (8%)	9 (7%)	0·679 (-0·05 – 0·07)
IV Piperacillin-Tazobactam, Nº (%)	3 (2%)	0 (0)	0·085 (-0·003 – 0·05)
IV Cefuroxime, Nº (%)	0 (0)	5 (4%)	0·023 (-0·07 - -0·01)
Other antibiotic, Nº (%)	3 (2%)	0 (0)	0·085 (-0·003 – 0·05)
IV Vitamin K prophylaxis, Nº (%)	120 (85%)	123 (89%)	0·316 (-0·12 – 0·04)
IV Vitamin K treatment, Nº (%)	10 (7%)	8 (6%)	0·660 (-0·04 – 0·07)
IV Caffeine citrate prophylaxis, Nº (%)	53/140 (38%)	57/137 (42%)	0·524 (-0·15 – 0·08)
Number of Caffeine doses, mean (SD)	6 (4.2%)	7.4 (4.0)	0·091 (-2·93 – 0·22)
IV Aminophylline prophylaxis, Nº (%)	62 (44%)	46 (33%)	0·068 (-0·01 – 0·22)
Number of Aminophylline doses, mean (SD)	8.4 (4.9)	8.2 (5.6)	0·855 (-1·83 – 2·20)
IV Phenobarbitone for seizures, Nº (%)	2 (1%)	1 (1%)	0·574 (-0·02 – 0·03)
Multivitamins, Nº (%)	72/140 (51%)	72/137 (53%)	0·851 (-0·13 – 0·11)
Folic acid, Nº (%)	79 (56%)	80 (58%)	0·743 (-0·14 – 0·10)
Iron supplements, Nº (%)	10 (7%)	18 (13%)	0·980 (-0·13 – 0·01)

a) Significance level and 95% confidence intervals determined by 2-sample proportion test for categorical variables and 2-sample t test for continuous variables.

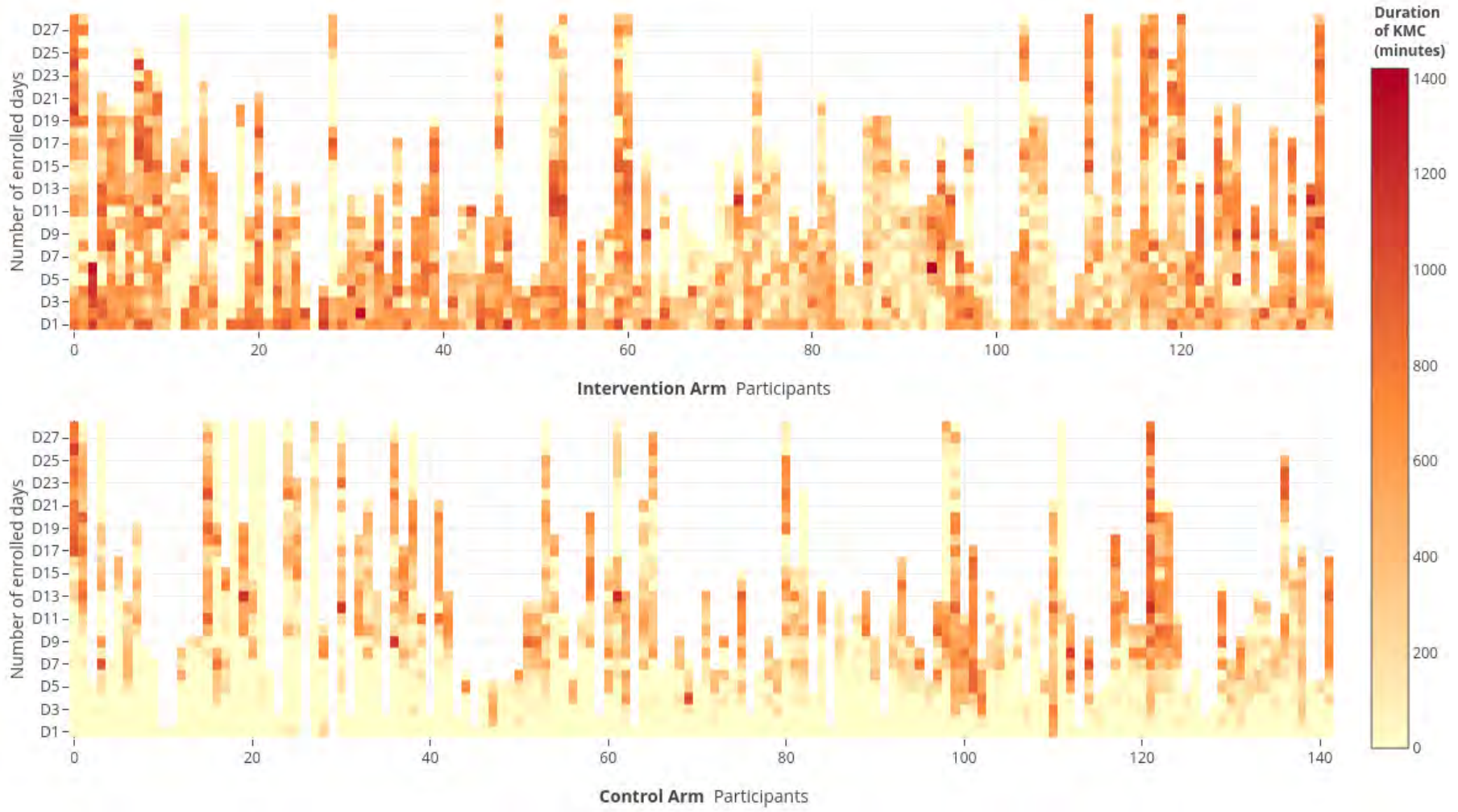
Abbreviations: bCPAP = bubble continuous positive airway pressure; CI = Confidence intervals; SD = Standard deviation

Online only figures



a) Criteria added or amended to increase relevance of aPSBI criteria to hospitalised neonates <2000g receiving KMC. Note – isolated apnoea refers to apnoea not temporally associated with milk aspiration or hypoglycemia.
Abbreviations: aPSBI = adapted Possible Serious Bacterial Infection; CPAP = Continuous positive airway pressure; h= hours; HR= heart rate; KMC= Kangaroo mother care; MRCG; Medical Research Council Unit The Gambia at LSHTM; NNU; Neonatal unit; RR=Respiratory rate; SpO_2= Oxygen saturation

e-Figure 1. Overview of eligibility criteria, study procedures and key definitions for eKMC trial



e-Figure 2. Duration (minutes) spent in kangaroo position, by allocation arm and day of enrolment

Checklist of items to include when reporting a randomized trial (56-58)

PAPER SECTION And topic	Item	Description	Reported on page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	1
INTRODUCTION Background	2	Scientific background and explanation of rationale.	5
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	5 - 6
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	7
Objectives	5	Specific objectives and hypotheses.	5
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	7 - 8
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	9
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (*e.g.*, blocking, stratification).	6
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	9
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	9
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.	9
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	9
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	10
Recruitment	14	Dates defining the periods of recruitment and follow-up.	10
Baseline data	15	Baseline demographic and clinical characteristics of each group.	10
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat" . State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).	10
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).	10
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	10
Adverse events	19	All important adverse events or side effects in each intervention group.	11
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	11 - 14
Generalizability	21	Generalizability (external validity) of the trial findings.	14
Overall evidence	22	General interpretation of the results in the context of current evidence.	14