STUDY PROTOCOL

The OMWaNA Study:
Operationalising kangaroo **M**other care before stabilisation amongst low birth **W**eight **N**eonates in **A**frica: a multi-site randomised controlled trial to examine mortality impact in Uganda

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Statement of Compliance

By my signature below, I hereby confirm that the study will be conducted in accordance with this protocol and in compliance with the tripartite harmonized ICH Guideline for Good Clinical Practice 1996 and the version of such protocol agreed to by the applicable regulatory authorities and approved by all Institutional Review Board and Ethical Committees.

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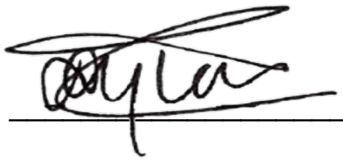
Name: Joy Lawn Signature:  Date: 1/7/20

Please note that study responsibilities are documented in the Trial Master and Investigator Site Files.

Contents

List of Abbreviations

AE	Adverse event
bpm	Beats per minute
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous positive airway pressure
cUS	Cranial ultrasound
d	Day(s)
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
EH	Entebbe Regional Referral Hospital
FGD	Focus group discussion
g	Grams
GCP	Good Clinical Practice
HR	Heart rate
h	Hour(s)
IH	Iganga District Hospital
ID	Identification
IDI	In-depth interview
IRB	Institutional Review Board
ICH	International Conference on Harmonisation
IV	Intravenous
IVH	Intraventricular haemorrhage
JH	Jinja Regional Referral Hospital
KNRH	Kawempe National Referral Hospital
LBW	Low birthweight
LMIC	Low- and middle-income countries
LSHTM	London School of Hygiene and Tropical Medicine
KMC	Kangaroo mother care
MH	Masaka Regional Referral Hospital

MIRI	Maternal Infant Responsiveness Instrument
MRC/UVRI	Medical Research Council/Uganda Virus Research Institute Uganda Research Unit in Entebbe
OMWaNA	'**O**perationalising kangaroo **M**other care before stabilisation amongst low birth **W**eight neonates in **A**frica'
PI	Principal Investigator
PIS	Participant information sheet
PSBI	Possible serious bacterial infection
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious adverse event
SGA	Small for gestational age
SOP	Standard operating procedure
SpO_2	Oxygen saturation measured by pulse oximetry
SSC	Skin-to-skin contact
TMF	Trial Master File
TSC	Trial Steering Committee
UgSh	Ugandan Shillings
WCI	Women's Capabilities Index
WHO	World Health Organization

Definitions

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject administered an experimental therapy, which does not necessarily have to have a causal relationship with this therapy (1)
APGAR score:	System for assessing newborns and response to neonatal resuscitation at the time of delivery; includes 5 components: 1) colour, 2) heart rate, 3) reflexes, 4) muscle tone, 5) respiration; each component is scored 0 to 2 at 1 and 5 minutes post-birth, and at 5-minute intervals thereafter up to 20 minutes for infants scoring <7 (2)
Apnoea:	No spontaneous breathing for 20 seconds, or less than 20 seconds and accompanied by colour change, oxygen desaturation (SpO_2 <88%), or bradycardia (HR <100 bpm)
Kangaroo mother care:	Package of care that consists of prolonged skin-to-skin contact between neonate and caregiver, usually the mother; promotion of exclusive breast milk feeding; early hospital discharge; and adequate support and close follow-up at home (3) **Continuous KMC:** Skin-to-skin contact between baby and caregiver for at least 18h/day **Intermittent KMC:** Skin-to-skin contact between baby and caregiver for periodic times of at least 1h duration per session
Low birthweight:	Birthweight <2500g; can be sub-categorised as follows (4): **Very low birthweight:** birthweight <1500g **Extremely low birthweight:** birthweight <1000g
Neonatal mortality rate:	Number of neonates dying before reaching 28 days of age, per 1,000 live births in a year (5)
Neonatal period:	First 28 days post-birth; can be sub-categorised as follows (6): **Early neonatal period:** 0-6 days post-birth **Late neonatal period**: 7-28 days post-birth
Preterm:	Birth at <37 completed weeks gestation; can be sub-categorised as follows (7): **Extremely preterm:** birth at <28 completed weeks **Very preterm:** birth at 28 to <32 completed weeks **Moderate to late preterm**: 32 to <37 completed weeks
Serious adverse	Any untoward medical occurrence which: (1)

event:	a) Results in death b) Is life threatening c) Requires prolongation of hospitalisation d) Results in persistent or significant disability/incapacity e) Requires intervention to prevent permanent impairment or damage
INCLUSION CRITERIA	
Indication for KMC "uncertain" according to WHO guideline concerning clinical stability (8):	Pragmatically defined as receiving ≥1 of the following therapies: • Supplemental oxygen: oxygen from cylinder, compressor or wall, which is delivered via nasal cannula, mask, or tent • Continuous positive airway pressure (CPAP): method of maintaining low pressure distension of lungs during inspiration and expiration when infant is breathing spontaneously (9) • Intravenous (IV) fluids: solution, typically containing dextrose and/or electrolytes, that is delivered directly to veins; indicated for neonates unable to take adequate enteral feeds • Therapeutic antibiotics: antibiotics given only for presumed or confirmed infection (not empirically/prophylactically) • Phenobarbital: medication used to treat neonatal seizures
EXCLUSION CRITERIA	
Severely lifethreatening clinical instability:	Defined as SpO_2 <88% in oxygen AND ≥1 of: • Respiratory rate <20 or >100 breaths/min • Apnoea requiring bag-mask ventilation • HR <100 or >200 bpm
Major congenital malformation:	A malformation that is present at birth and which is incompatible with life or requires immediate surgical management
Severe jaundice:	Jaundice occurring within the first 24h after delivery and/or visible in sclera, palms or soles
PRIMARY OUTCOME	

Early neonatal mortality:	Death of a neonate within the first 7 days after birth (day 0-6)
SECONDARY OUTCOMES	
Hypothermia:	Axillary temperature below the normal range (36.5°C – 37.5°C); can be subcategorised as follows: Mild: 36.0°C – 36.4°C Moderate: 32.0°C – 35.9°C Severe: <32°C
Duration of hospital admission:	Mean time (days and hours) from hospital admission to discharge
Breastmilk feeding:	Process of feeding a mother's breastmilk to her infant, either directly from the breast or by expressing milk from the breast and feeding it to the infant by nasogastric tube, bottle, cup, or spoon, to provide calories, macronutrients, and micronutrients (10)
Time from intervention/control procedures starting to exclusive breastmilk feeding:	Mean time (days and hours) from initiation of intervention/control procedures to exclusive breast milk feeding
Neonatal mortality:	Death of a neonate within the first 28 days of life
Time from intervention/control procedures starting to clinical stabilisation:	Mean time (days and hours) from initiation of intervention/control procedures to clinical stabilisation, with stability defined as having met the following criteria for a continuous period of at least 24h: (i) Breathing spontaneously with SpO_2 >90% in room air (ii) No need for supplemental oxygen or CPAP (iii) Respiratory rate 40 to <60 breaths per minute (iv) No apnoea (v) Heart rate 80 to <180 beats per minute (vi) Axillary temperature 36.0 to 37.4 degrees Celsius (vii) No need for IV fluids
Time from intervention/control procedures starting to death:	Mean time (days and hours) from initiation of intervention/control procedures to death

Frequency of readmission:	Mean frequency of episodes in which an infant who had been discharged from a hospital is admitted again during a defined time period
Daily weight gain:	Mean daily weight gain (g/day) during a defined time period
Infant-caregiver attachment:	Assessed using the Maternal Infant Responsiveness Instrument (MIRI), a 22-item questionnaire measuring maternal responsiveness to infant cues (11,12); initially developed in the United States and being used in Uganda
Women's well-being:	Assessed using the Women's Capability Index (WCI), a composite measure of quality of life that will capture the broader benefits to the mother of practising KMC compared to standard care (13); originally developed in Malawi, and now being adapted and tested for use in Uganda
OTHER PROCESS OUTCOMES	
Cardio-respiratory stability:	Proportion of time spent with suboptimal HR (<100bpm) and SpO_2 (<85%) over the first 24h post-randomisation, measured and recorded continuously using pulse oximetry.
Hypothermia density:	Proportion of time temperature <36.5°C during a defined time period
Presence and severity of intraventricular haemorrhage (IVH):	Complication of prematurity characterised by bleeding within the ventricles (fluid-filled areas) inside the brain, typically originating from the periventricular germinal matrix (a highly vascular collection of neuronal-glial precursor cells); majority of affected infants are asymptomatic; diagnosis is based on screening cranial ultrasound; severity ranges from grade 1 (mild) to grade 4 (severe) (14)
Presence of late intracerebral sequelae of prematurity:	Late intracerebral sequelae of prematurity may include, but are not limited to the following: cystic degeneration, cerebral atrophy, post-haemorrhagic hydrocephalus
Hypoglycaemia:	Blood glucose level <2.6 mmol/L, as measured by bedside testing

Executive Summary

Globally, an estimated 2.5 million neonatal deaths occurred in 2017 (15). Over 80% of these deaths occurred in babies who are small at birth, due to prematurity and/or being small for gestational age (SGA) (16). Major mortality reductions could be achieved by improving care of small neonates in lowresource settings (16–18). Kangaroo mother care (KMC) consists of skin-to-skin positioning (e.g., with the mother), breastfeeding, and supportive care (3,19). The most recent Cochrane review and a metaanalysis demonstrated that KMC is associated with decreased mortality (20,21), sepsis (20,21), hypothermia (20,21), and length of stay (20) amongst *stable* neonates ≤2000 grams (g). The World Health Organization (WHO) recommends KMC for the "routine care of newborns weighing ≤2000g initiated as soon as newborns are clinically stable" (8).

However, estimates suggest that ≥75% of neonatal deaths occur *before stabilisation* in settings without intensive care (16,17,22). The only randomised controlled trial (RCT) evaluating the effect of KMC on mortality in neonates before stabilisation, from Ethiopia, reported decreased mortality but had methodological issues (23). Among 17 RCTs (14 enrolled only stable neonates) comparing KMC with standard care (incubators or radiant heaters) in low birthweight (LBW, <2500g) neonates aged <15 days, there was significant variability in how clinical stability was defined, with three providing no definition at all. Hence codifying stability criteria for KMC is critical. Recent WHO guidelines for preterm care have prioritised determining the effect of KMC initiated prior to stabilisation on neonatal mortality as a key evidence gap (8).

The OMWaNA study is a partnership between the Medical Research Council/Uganda Virus Research Institute (MRC/UVRI), the London School of Hygiene & Tropical Medicine (LSHTM) and Makerere University and includes a RCT with accompanying process and economic evaluations. The primary aim of the trial is to examine the impact of KMC initiated before stabilisation on mortality within 7 days relative to standard care amongst neonates ≤2000g at four hospitals in Uganda.

The primary objective of the study is to:

1. Determine the effect of KMC initiated before stabilisation on mortality within 7 days relative to standard care amongst neonates ≤2000g.

The secondary objectives are to:

1. Determine the effect of KMC initiated before stabilisation on other important clinical outcomes relative to standard care amongst neonates weighing ≤2000g.
2. Estimate the incremental costs and cost-effectiveness of KMC initiated before stabilisation relative to standard care from the societal perspective.
3. Explore causal pathways for the clinical effects of KMC initiated before stabilisation relative to standard care amongst neonates weighing ≤2000g.
4. Examine the barriers and facilitators to initiating KMC before stabilisation to inform uptake and sustainability in Uganda.

We will conduct an individually randomised, controlled, superiority trial with two parallel groups; an intervention arm allocated to receive KMC and a control arm receiving 'standard' care. Given the nature of the KMC intervention, blinding parents/participants is not possible. Process and outcome data will be anonymised, and all analyses will be blinded. We will enrol neonates before stabilisation for whom the indication for KMC is currently "uncertain," defined as receiving ≥1 medical therapy [e.g., intravenous

(IV) fluids, oxygen to support breathing] in accordance with the WHO Practical Guide for KMC (3). The uncertainty principle states that, if a provider is uncertain about which treatment is best for a patient, "offering the patient randomisation to equally preferred treatments is acceptable" (24). This principle has been used as an eligibility criterion in many large trials (24). The trial's primary outcome is mortality within 7 days. Secondary outcomes include prevalence of hypothermia at 24 hours post-randomisation; mean time from intervention/control procedures starting to clinical stabilisation or death; mean duration of admission; mean time from intervention/control procedures starting to exclusive breastmilk feeding; mortality within 28 days; mean frequency of readmission; and mean daily weight gain, infant-caregiver attachment, and women's well-being at 28 days.

1. Hypothesis, aim, objectives, and outcomes

1.1 Aim

To examine the impact of KMC initiated before stabilisation relative to standard care amongst neonates ≤2000g at four hospitals in Uganda.

1.2 Primary Hypothesis for the trial

Neonates ≤2000g in the arm allocated to receive KMC before stabilisation will have a 25% overall reduction in mortality within 7 days compared to neonates allocated to receive standard care.

1.3 Objectives

The primary objective of the study is to:

1. Determine the effect of KMC initiated before stabilisation on mortality within 7 days relative to standard care amongst neonates weighing ≤2000g.

The secondary objectives of the study are to:

1. Determine the effect of KMC initiated before stabilisation on other important clinical outcomes relative to standard care amongst neonates weighing ≤2000g.
2. Estimate the incremental costs and cost-effectiveness of KMC initiated before stabilisation relative to standard care from the societal perspective.
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4. Examine the barriers and facilitators to initiating KMC before stabilisation to inform uptake and sustainability in Uganda.

1.4 Outcomes for the trial

1.4.1 Primary outcome

The primary outcome is early neonatal mortality, defined as mortality within 7 days.

1.4.2 Secondary outcomes

- Prevalence of hypothermia at 24 hours post-randomisation
- Mean duration of hospital admission (days and hours)
- Mean time from intervention/control procedures starting to exclusive breastmilk feeding (days and hours)
- Mortality within 28 days
- Time from intervention/control procedures starting to clinical stabilisation (days and hours)
- Time from intervention/control procedures starting to death (days and hours)
- Frequency of readmission
- Mean daily weight gain (g/day) at 28 days
- Infant-caregiver attachment at 28 days
- Women's well-being at 28 days

2. Background

2.1 Kangaroo Mother Care to Improve Neonatal Survival

Each year, 15 million babies are born preterm (<37 completed weeks gestation) and 1 million deaths occur as a direct result of complications of preterm birth (16,17,25). Sub-Saharan Africa and South Asia account for three-quarters of the 2.6 million neonatal deaths that occur annually, and preterm birth is the leading cause of these deaths (15). Progress in preventing preterm birth has been limited, but major reductions in mortality could be achieved by improving care in low-resource settings (16,17,26,27). In such settings, 50% of neonates born at 32 to 34 weeks gestation, a time when nearly all should survive, die because newborn special care is not available (17,22). KMC is a package of care, which consists of: early, continuous, and prolonged skin-to-skin contact (SSC), usually with the mother; promotion of exclusive breast milk feeding; early hospital discharge; and adequate support and close follow-up at home (3). The most recent Cochrane review and a meta-analysis demonstrated that KMC among *stable* neonates ≤2000g is associated with decreased mortality (RR 0.60-0.64) (20,21), sepsis (RR 0.35-0.53) (20,21), hypothermia (RR 0.22-0.28) (20,21), hypoglycaemia (RR 0.12) (21), and length of stay (mean difference -1.61 days) (20) compared to conventional care. WHO guidelines recommend KMC for "routine care of newborns weighing ≤2000 grams (g)… initiated as soon as newborns are clinically *stable*" (8), where stability has been defined as vital functions (breathing, circulation) not requiring "continuous medical support and monitoring," and not being "subject to rapid and unexpected deterioration" (5).

KMC works through multiple pathways, many of which are mediated by skin-to-skin contact triggering a primary neuro-endocrine mechanism involving oxytocin as a key mediator with systemic effects in both mother and neonate. The key causal pathways underpinning the protective benefit of KMC are: thermal control; reduction in cortisol and stress response; cardio-respiratory stabilisation; enhanced breastmilk supply and breastmilk feeding; and empowering the mother as key carer for her baby. Although previously extensively researched in stable babies receiving skin-to-skin contact, the validity and relative contribution of these pathways in skin-to-skin contact in neonates prior to stability is not fully known. Further research is therefore warranted to improve our understanding of the physiological processes underpinning any potential benefit of KMC in this population.

2.2 Gaps in the Evidence regarding Kangaroo Mother Care

Estimates suggest that ≥75% of neonatal deaths occur *prior to stabilisation* in settings without intensive care (16,17,22). A notable gap exists in the evidence supporting the use of KMC in this vulnerable population. The only RCT of KMC in neonates before stabilisation with mortality outcomes was conducted in Ethiopia (123 neonates ≤2000g) and reported major mortality impact [RR 0.57, 95% confidence interval (CI) 0.33-1.00] (4)] (23). Notably, this trial excluded >50% of eligible neonates, did not utilise allocation concealment, and had an apparent imbalance between groups (favouring KMC) at baseline, with a greater proportion of those receiving standard care being born at gestational ages (GA) <32 weeks or weighing <1250g (4,9). Among 17 RCTs (14 enrolled only 'clinically stable' neonates) comparing KMC with conventional care in low birthweight (LBW, <2500g) neonates aged <15 days, there was significant variability in how clinical stability was defined. Six defined this based on therapies (28–33), five on 'hemodynamic stability' (23,34–37), and three on specific vital sign parameters (38–40), while three provided no definition at all (41–43). Hence codifying stability criteria for KMC is critical. A recent WHO guideline for care of preterm neonates highlighted evidence gaps regarding the effect of KMC on mortality amongst neonates that are not yet stable. These included absence of criteria to

identify which neonates are *stable enough* to safely receive KMC; the optimal time for initiation; and the duration required to reduce mortality (8).

There are few published economic evaluations of KMC, and none conducted rigorously in low-income countries from a societal perspective, or with systematic equity assessment. Cost analyses have consistently found that KMC for LBW neonates resulted in cost savings for the hospital or provider relative to conventional care but have not considered whether KMC may increase costs to households nor specifically considered KMC initiated before stabilisation. Such studies have included a multi-centre RCT in Mexico, Ethiopia, and Indonesia (29), an RCT at one hospital in Colombia (44), and implementation studies in one Nicaraguan (45) and one Brazilian hospital (46), all of which compared costs of KMC and standard care in LBW neonates; and an evaluation of a programme to increase overall rates of KMC and breastfeeding at 18 neonatal units in the UK (47).

2.3 Neonatal Care in Sub-Saharan Africa and Uganda

Compared to other regions of the world, sub-Saharan Africa has experienced slow progress towards reducing neonatal mortality, particularly mortality due to preterm birth (25). This is likely to be due to higher preterm prevalence and lower access to care (17,22), and shortages of neonatal healthcare providers (18,48). Further, many interventions are introduced to low-resource settings without adequate evidence of their effectiveness in such settings (17,18). Incubators, the standard mode of thermal support for small and preterm neonates, are often unavailable or fail to function due to resource-related difficulties such as inconsistent electricity supply or access to replacement parts. Further, they require regular disinfection; however, this is often not done in resource-constrained settings (49). Other potential issues include risk of cross-infection from other neonates when incubators are shared, and cost (50–52).

Over the past decade in Uganda, the neonatal mortality rate has remained relatively stagnant (27-28 deaths per 1,000 live births), while under-5 mortality declined from 83 to 64 deaths per 1,000 live births over the same period (53). In Uganda alone, an estimated 36,000 newborn deaths occur annually (15), over a quarter of which are due to complications of prematurity (54). In 2006, the Ugandan government established a Newborn Steering Committee, which advised immediate action to increase the scale-up of KMC in facilities (55), and all district hospitals now have KMC. Evidence for the large-scale effectiveness and sustainability of KMC is lacking (17,18). This trial will address these evidence gaps and results may facilitate further scale-up in Uganda and in similar hospital contexts elsewhere.

2.4 Formative Work

A study demonstrating the feasibility of KMC initiated prior to stabilisation amongst neonates ≤2000g was undertaken at Jinja Regional Referral Hospital in Uganda in 2016, led by Dr Medvedev (Morgan). The findings, which are summarized below, were published in the *Journal of Global Health* in 2018 (56).

Finding 1: Sufficient numbers of neonatal admissions met eligibility criteria: To determine the number of eligible neonates, audit data were collected on neonates admitted between June 2015 and May 2016. We also reviewed current practices to inform coding of neonates as 'before stabilisation,' i.e., for whom the indication for KMC is currently "uncertain." A total of 268 charts were reviewed, among which 254 met birthweight criteria and were complete. Amongst these, 226 (89%) were receiving ≥2 care therapies (Table 1). Among neonates who received only one therapy, the majority received empiric antibiotics because they were at risk of infection (i.e., not given for suspected or confirmed infection), a common practice in preterm/LBW neonates and frequently given to newborns considered stable. For

this reason, this enrolment criterion has been modified to receipt of ≥1 therapy excluding empiric antibiotics. Hence based on admission data in JH showing ~480 neonates ≤2000g, we anticipate ≥400 admissions to be eligible each year at JH (see Section 10.1 for information on other sites).

Table 1: Number of care therapies received amongst neonates in admissions audit (N=254)

Number of therapies received*	Frequency (%) of ≤2000g neonates N=254	95% CI	Frequency (%) of <1500g neonates n=110	95% CI	Frequency (%) of <1000g neonates n=29	95% CI
0 to 1	29 (11.4)	7.8-16.0	11 (10.0)	5.1-17.2	3 (10.3)	2.2-27.4
2	73 (28.7)	23.3-34.7	32 (29.1)	20.8-38.5	4 (13.8)	3.9-31.7
3	105 (41.3)	35.2-47.7	47 (42.7)	33.3-52.5	19 (65.5)	45.7-82.1
4 to 5	47 (18.5)	13.9-23.8	20 (18.2)	11.5-26.7	3 (10.3)	2.2-27.4

*Oxygen, IV fluids, phenobarbital, antibiotics (empiric or for presumed/confirmed infection)

Finding 2: Monitoring and provision of concurrent care therapies was feasible in the KMC position: To demonstrate the feasibility of monitoring and providing care therapies (oxygen, IV fluids, etc.) in the KMC position, we enrolled a sample of 10 neonates meeting proposed trial eligibility criteria between July and December 2016. Gestational age was determined by Ballard examination (57). Mothers were counselled to provide KMC ≥18h per day. During interruptions when mothers carried out activities like bathing, a family member was encouraged to provide KMC. If none was available, the neonate was placed in an incubator until the mother returned. Neonates were otherwise managed according to unit guidelines. All neonates received continuous monitoring of SpO_2 and HR.

Among the 10 neonates enrolled, median birthweight was 1310g [interquartile range (IQR) 820-1600g], median gestational age was 28 weeks (IQR 26-31 weeks), and median length of stay was 10 days (IQR 9-14 days). Eight neonates were discharged home and two died. Both neonates that died were extremely premature (26-27 weeks) and extremely LBW (700-750g), thus at very high risk of death, particularly in a low-resource setting given the lack of ventilatory support and other intensive care usually required for survival at this gestational age. The median duration of individual KMC episodes ranged from 115 to 134 minutes, and the median daily duration ranged from 4.5 to 9.7 hours, with a slight upward trend over time. Two neonates received the target duration of 18 hours of KMC on day 1 (18.1 and 21.6 hours) and one neonate received the target duration on day 5 (18.3 hours) (see Section 17 for discussion about KMC compliance). The mean number of care therapies received ranged from 3.7 to 4.1 per day across the first 14 days, and the number of therapies a neonate was receiving did not affect the daily duration of KMC. Continuous SpO_2 monitoring was conducted throughout the enrolment period for all participants, and providers did not report any problems with monitoring or care provision.

Finding 3: KMC (prior to stabilisation) and randomisation were acceptable to parents and providers: From May to July 2016, we interviewed 10 parents (8 mothers, 2 fathers, different to those above) and 10 providers (8 nurses, 2 doctors) to evaluate acceptability of KMC for neonates prior to stabilisation. Over 80% of stakeholders reported acceptability of KMC among neonates <48 hours post-birth who are receiving other therapies. A few mothers expressed concern that KMC might cause pain or displace IV/oxygen tubing, as also found in KMC studies in high-income settings (58,59). Parents and providers suggested that KMC practice could be improved through staff and peer-counselling, more beds/space, and improved availability of monitoring devices. All providers and parents were eager to participate in trials. Eighty percent of providers and 50% of parents expressed willingness to randomise neonates.

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

Two clinical trials with similar objectives and outcomes to the OMWaNA trial are currently in progress in The Gambia [eKMC (60)] and multiple LMICs [(Ghana, India, Nigeria, Malawi, Tanzania); I-KMC (61)], and are investigating the use of early (started at <24h of admission) and immediate (started within 2h of birth) KMC, respectively, compared to standard care (KMC initiated at >24h of admission) in mild to moderately unstable hospitalised neonates. The eKMC lead investigator, Helen Brotherton, is a collaborator on the OMWaNA trial, and learning from the eKMC trial has informed the development of the OMWaNA trial protocol. Efforts to align study processes and outcomes have been made to maximise our understanding of the impact of this intervention.

2.5 Rationale for the OMWaNA study

Globally, there are 2.6 million neonatal deaths each year, and most of these deaths occur in small neonates before stabilisation. The OMWaNA trial aims to assess the effectiveness of KMC in reducing mortality in a population where the benefits of KMC are currently uncertain, a finding that would have important implications for global health policies. The OMWaNA trial is innovative in that it will allow us to determine the effect of KMC initiated before stabilisation on neonatal mortality within 7 days. By comparing the incremental cost and cost-effectiveness of KMC relative to standard care, this trial will be the first to assess the value for money of KMC. These findings will be crucial to help ensure the sustainability of this intervention. In addition, as part of the wider study we will use data from the trial to explore the physiological mechanisms by which KMC may reduce mortality, which have been poorly researched to date.

3. Study Setting and Design

3.1 Study Setting

The host institution for the trial will be the MRC/UVRI and LSHTM Uganda Research Unit in Entebbe. The trial willl be undertaken in collaboration with Makerere University and LSHTM. These institutions are internationally recognised centres of excellence for research, with significant experience conducting and monitoring RCTs.

The study will be conducted in five sites in Uganda:

- Jinja Regional Referral Hospital (JH)
- Masaka Regional Referral Hospital (MH)
- Entebbe Regional Referral Hospital (EH)
- Iganga District Hospital (IH)
- Kawempe National Refferal Hospital (KNRH)

JH, EH, and IH each provide care to ~5,000 to 6,000 neonates per year. MH provides care to ~10,000 neonates per year, and KNRH provides care to ~8,000 neonates per year. Current practice at these sites is to provide KMC for stable neonates ≤2000g, according to WHO guidelines. MH, EH, and KNRH have research linkages with MRC/UVRI, and JH and IH have linkages with Makerere. Makerere has established health surveillance systems in the Busoga region where JH/IH are located.

3.2 Design of the Trial

This is a four-centre, individually randomised, controlled, superiority trial with two parallel groups; an intervention arm allocated to receive KMC and a control arm allocated to receive 'standard' care.

3.2.1 Randomisation

Treatment allocation will be random and in a 1:1 ratio between groups. The random allocation sequence will be computer generated centrally at LSHTM stratified by birthweight (<1000, 1000-1499, or ≥1500g) and recruitment site. Birthweight is an important predictor of newborn survival. Neonatal mortality is 2-fold higher in SGA term neonates and 15-fold higher in SGA preterm neonates compared to appropriately sized term neonates (16). At each site, a laptop will be programmed with the random allocation sequence. This will be done in RedCap to avoid any possibility of viewing the allocation sequence. Allocation will only be revealed after the study medical officer at the site has completed entry of the mother's and neonate's details and all required screening data (see Section 5.3) into RedCap. The entry details will then be transferred to MRC/UVRI. Each site will have one spare laptop in case of breakdown or theft; if both fail, the site will revert to random allocation using telephone as the back-up option.

3.2.2 Blinding

Given the nature of the KMC intervention, blinding parents/caregivers is not possible. Process and outcome data will be anonymised, and all analyses will be blinded.

3.2.3 Details of the Intervention arm

Neonates randomised to the intervention group will receive KMC along with conventional therapies (e.g., IV fluids, antibiotics, oxygen) delivered according to standardised clinical guidelines (see Section 3.2.5). Parents will be encouraged to provide KMC as close to continuously as possible. While we anticipate the mother will be the primary KMC provider, a family member or close friend (helper) may also provide KMC. For interruptions due to mothers carrying out activities like bathing and going to the rest room, a family member or helper will be encouraged to take over KMC while the mother is away If the mother has no family member or helper to continue KMC, the baby will be placed into an incubator or radiant heater according to standard care until the mother or another family member returns.

KMC will continue to be encouraged until discharge and at home after discharge, as per WHO guidelines (commonly practised until the baby is 2500g or around their due date or resists the KMC position, and this is often for 4 to 10 weeks).

3.2.4 Details of the Control arm

Infants randomised to the control group will receive standard neonatal care for that centre. Incubators and radiant heaters are the standard mode of thermal support for small and preterm neonates. It is common practice for several babies to share a single incubator. Conventional therapies will be administered according to standardised guidelines, as in the intervention arm. These include IV fluids (given by bolus or burette), respiratory support with nasal cannula oxygen and CPAP, first line IV antibiotics (ampicillin and gentamicin), and first line anti-seizure medications (phenobarbital). Feeding support in small and preterm infants is typically via nasogastric tube, spoon, syringe or cup. Infants in the control group can transition to routine (intermittent) KMC once stable (see Section 3.2.5), in line with study site standard clinical procedures.

3.2.5 Clinical Stability Criteria

Neonates will be considered stable when the following criteria have been met for a continuous period of at least 24h [criteria consistent with the WHO I-KMC trial (61)]:

(i) Breathing spontaneously with SpO_2 >90% in room air

(ii) No need for supplemental oxygen or CPAP

(iii) Respiratory rate 40 to <60 breaths per minute

(iv) No apnoea

(v) HR 80 to <180 beats per minute

(vi) Axillary temperature 36.0 to 37.4 degrees Celsius

(vii) No need for IV fluids

3.2.6 Concomitant Therapies and Medications

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

3.3 Design of the Economic Evaluation

The incremental cost, cost-effectiveness, budget impact, and equity of KMC for neonates before stabilisation relative to standard care, from the societal perspective (provider and household combined) will be examined, along with the effects of the intervention on both the health of babies (measured in disability-adjusted life-years, DALYs) and the wellbeing of the mothers and babies in the study. The economic evaluation will respond to decision makers' key policy questions regarding KMC and adhere to the principles, methodological specifications, and reporting standards of the latest reference cases for economic evaluations (62,63). Both financial costs – actual monies paid – and economic costs – the full value of all resources used – will be assessed. We will consider cost variation (e.g., between hospitals) and how costs may differ outside the trial setting.

We will utilise the Women's Capabilities Index (WCI) to assess women's well-being (13). The WCI is a multidimensional measure based on Sen's capability framework for assessing women's quality of life. Originally developed in Malawi, the WCI is now being adapted and tested for use in Uganda. It is an innovative composite measure of quality of life that will allow the broader benefits to the mother of practising KMC compared to standard care to be captured.

3.4 Design of the Process Evaluation

The process evaluation will explore causal pathways for the clinical effects of KMC initiated before stabilisation relative to standard care (Objective 2) and examine barriers and facilitators to initiating KMC before stabilisation to inform uptake and sustainability in Uganda (Objective 3). This evaluation

will consider both intended (beneficial) and unintended (negative) clinical effects, assessing how and why effects were attained and what systems changes will be required by whom as a result. The process evaluation will include focus group discussions (FGD) with neonatal healthcare providers, parents (intervention and control arms), and hospital administrators after 6 and 18 months of recruitment. In-depth interviews (IDI) with mothers will explore social and cultural factors that may influence maternal coping and compliance with care recommendations. IDIs with parents whose babies died during the hospital stay, including those who experienced a death in the KMC position, will explore parental experiences of trauma and bereavement. The process evaluation will include four phases (64):

1) Design
2) Pilot
3) Evaluation
4) Formation of recommendations to improve uptake (if intervention is found to be beneficial)

The process evaluation will be designed with stakeholder inputs, conducting two half-day workshops prior to the start of the trial at MRC/UVRI in Entebbe. The first workshop will include district health authorities, local community leaders, paediatricians, newborn nurses, and parents. The second will include local academics (MRC/UVRI, Makerere University), professional health organisations (Uganda Paediatric Association), and national (Ministry of Health) and international (UNICEF, International KMC Network) policy-makers.

4. Selection and Withdrawal of Participants

4.1 Participants

The trial will include neonates born weighing ≥700g and ≤2000g, aged >1 and <48 hours, and for whom the indication for KMC is "uncertain" according to WHO guidelines concerning clinical stability (3). The process and economic evaluations (Objectives 2-4) will include administrators, providers, and parents of neonates at the four hospitals.

4.2 Eligibility Criteria for the Trial

Participants must meet the following inclusion criteria and not have any of the exclusion critieria to be able to participate in the trial.

4.2.1 Inclusion criteria

- Neonate admitted to JH, MH, EH, IH, or KNRH (inborn or outborn)
- Singleton, twin, or triplet (if triplet pregnancy resulted in demise/stillbirth of one or more fetuses)
- Birthweight ≥700g and ≤2000g
- Chronological age 1-48 hours at time of screening
- Alive at time of recruitment
- Parent/caregiver able and willing to provide KMC
- Parent/caregiver willing to attend follow-up visit
- Indication for KMC "uncertain" according to WHO guideline concerning clinical stability: pragmatically defined as receiving ≥1 therapy: oxygen, CPAP, IV fluids, therapeutic antibiotics, phenobarbital

4.2.2 Exclusion criteria

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

4.3 Eligibility Criteria for Focus Group Discussions and Interviews

Participants must meet the following inclusion and exclusion criteria to participate in FGDs and interviews.

4.3.1 Inclusion criteria

- Key stakeholder (parent of hospitalised neonate, neonatal healthcare provider (nurse or doctor), hospital administrator) at JH, MH, EH, IH, or KNRH
- Policy makers (WHO, UNICEF, Ministry of Health and Uganda Peadiatric Association member and other international bodies that support maternal and child health)
- ≥18 years of age (providers, administrators) or ≥15 years of age (parents)

4.3.2 Exclusion criterion

- Participant does not provide written informed consent to take part in FGD/interview (Appendix B)

4.4 Withdrawal of Participants

A study participant will be discontinued from participation in the study if any situation occurs such that continued participation in the study would not be in the best interest of the participant (see Section 9 for additional details). Participants are free to withdraw from the study at any time without giving a reason.

5. Study Procedures

All study procedures will be conducted in accordance with ICH-GCP principles and all research personnel involved in the study will undergo ICH-GCP training. Healthcare workers at the study sites will be trained on study objectives, overview of procedures, standardised management protocol and asked to inform study personnel of any potential participants and in the event of a clinical deterioration.

5.1 Internal Pilot

All study personnel will undergo training according to study specific procedures to ensure high quality recruitment, data collection, and intervention implementation (see Section 5.9). This will take place prior

to an internal pilot phase involving recruitment of 10 participants at each site; piloting of data collection tools and processes; and provision of the intervention alongside other medical therapies (e.g., oxygen, IV fluids). This will enable refinement of the study procedures and documentation. Initially, the internal pilot will take place at EH only. Once study personnel at EH demonstrate successful performance of trial procedures, the internal pilot phase will commence at the four remaining hospital sites (IH, JH, MH, KNRH). If procedures are judged to be adequate and in accordance with ICH-GCP principles, internal pilot participants will be included in the sample for the overall trial.

5.2 Screening

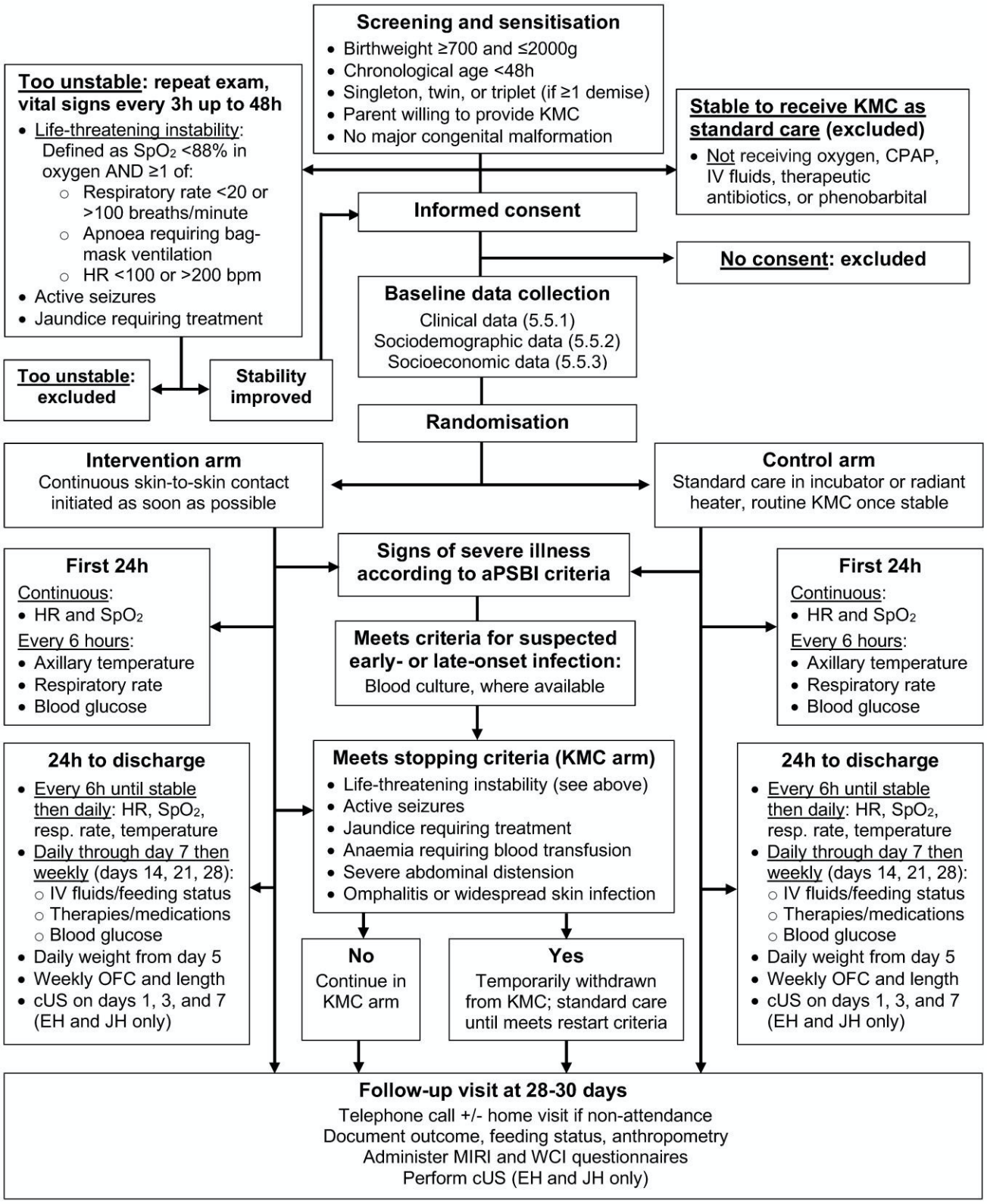
All new admissions to the newborn units at JH, IH, EH, KNRH and MH will be screened for eligibility by trained study staff. Eligibility will be assessed as soon as possible after admission and once the baby is aged 1h or older. This is in recognition of the large physiological changes that take place following delivery and that the stability of a newborn aged <1h may change rapidly and not accurately reflect the stability over the following 24h. All screening procedures will be performed by study nurses or medical research officers, with support from the study paediatrician at each site. Oral informed consent will be obtained from a parent/caregiver prior to the initiation of screening procedures.

Screening procedures will take place at the radiant heater or incubator where the neonate has been admitted in the following order:

1. Neonatal chronological age will be ascertained by questioning the parent/caregiver and/or examining the antenatal card, medical record, or referral notes.
2. Weight will be measured using the study scale (Seca) to ensure weight is ≥700g and ≤2000g.
3. A focused physical examination will be conducted to assess for the presence of visually recognisable major congenital malformations, severe jaundice, and seizures.
4. A pulse oximeter with neonatal probe will be attached for continuous monitoring and documentation of HR and SpO_2 for an initial 10 minutes.

5.3 Study Schedule

Figure 1. Study schedule with overview of procedures and evaluations



5.4 Recruitment

5.4.1 Sensitisation

General sensitisation will be conducted at the four study sites, surrounding antenatal clinics, and major referral centres, aiming to raise awareness of both KMC and the planned study. This will begin prior to the internal pilot and continue throughout the duration of the study.

Following identification of an eligible participant, initial sensitisation of the parent/caregiver will be done by telling them about the study and inviting them to participate.

5.4.2 Informed consent

Written informed consent will be sought from the parents of all participants for the following neonatal participation: inclusion in the study; collection of sociodemographic data; collection of clinical data; and randomisation to study arm. Consent will also be taken for the possibility that the parent/caregiver will provide continuous skin-to-skin contact, if randomised to that arm. Additionally, consent will be taken for the collection of household socioeconomic and cost data, as well as data on infant-caregiver attachment and women's well-being.

Medical officers or study nurses will obtain informed consent. The preferred person to provide informed consent for neonatal involvement is the mother. If a mother is unavailable or too ill to provide consent, informed consent will be obtained from the father. Once the mother is available and feeling well enough, the informed consent process will be repeated to confirm her consent for her baby's continued participation in the study.

Impartial and literate witness will be used during consent for illiterate parents, as per ICH-GCP guidance.

Further details regarding the informed consent process are detailed in section 14.5.

5.4.3 Enrolment

Following informed consent, a unique study identification number will be allocated, and the neonatal enrolment log will be completed. A separate maternal/caregiver enrolment number will be allocated, and a maternal/caregiver enrolment log sheet completed to identify and link the unique study ID numbers of parent/caregiver and neonate. This will include options for entering multiple caregivers, in the event of the mother not being available immediately and other family members providing the intervention.

5.5 Collection of Baseline Data

5.5.1 Clinical data

Study staff will collect the following clinical data as soon as possible after enrolment, with the exception of gestational age assessment and length measurement, which may be delayed to within 48h of admission. If any medical therapies (e.g., oxygen) have already been started by study staff, these will be continued throughout the clinical data collection process.

Research staff will be trained in appropriate infection control procedures and study specific protocols will detail infection control measures for the use of study equipment (pulse oximeters, weighing scales, etc.) to avoid cross-infection and contamination between participants.

- Axillary temperature will be measured with a digital thermometer (in degrees Celsius). Three measurements will be taken to enable calculation of the mean value.
- A capillary sample for blood glucose measurement will be obtained by heel prick using appropriately sized lancets and study-specific blood glucose machines at each site.
- Physical examination will be conducted.
- Head circumference [occipitofrontal circumference (OFC)] will be measured. • Gestational age will be estimated using the Ballard score (Appendix C)
- Crown-foot length will be measured.

The collection of baseline clinical data is estimated to take approximately 30 minutes, not including gestational age and length measurement. Data will be recorded in the eCRF (Appendix D) by trained study staff.

5.5.2 Sociodemographic data

Following the collection of baseline clinical data (with exception of gestational age and length measurement), trained study staff will collect the following sociodemographic data using standardised parent interviews and medical records (antenatal and hospital). Data will be recorded in the eCRF by trained study staff.

- Maternal details: contact details; date of birth; marital status; employment; highest level of education; date of last menstrual period (LMP); significant medical history; antenatal history (gravidity, parity, complications, interventions)
- Perinatal details: mode of delivery; presence of sepsis risk factors; administration of antenatal steroids and antibiotics in preceding 7d; APGAR scores; date and time of birth
- Neonatal details: gender; age at admission; admission diagnoses; multiple birth; interventions since birth (resuscitation, medications, other therapies)
- SARS-CoV-2 signs/symptoms and testing status/results for mothers and babies recruited after 25 March 2020

5.5.3 Socioeconomic Data

Trained study staff will collect the following socioeconomic data within 48h of admission, using standardised parent interviews. Data will be recorded in eCRF by trained study staff.

- Women's Capability Index: questionnaire to be administered to mothers immediately following collection of the above maternal sociodemographic data
- Household details: household density; number of children; occupation and highest educational level of other household members; data to be obtained as soon as is practical (may be collected after randomisation/allocation in order to avoid delays in starting intervention)

Trained study staff will also inform families that, over the coming month, they will be asked about their expenditures and the activities of members of their household (and any extended family members who become involved in care provision) in order to evaluate the economic impact of KMC relative to standard care. Data that will be collected includes the following:

- Expenditures: Medical supplies/hospital fees; food; transport
- Activities: Extent to which members of their household (and any extended family who become involved in care provision) were able to participate in their usual activities (paid work, household work, farming own land, or school/play) versus took time to care for/support the baby and/or parents, and any income/revenue lost as a result of this.

5.6 Randomisation

Randomisation will take place following collection of necessary baseline data and before the intervention or control procedures start. The details of the randomisation method are outlined in section 3.2.1. In situations where both twins are eligible for enrollment, they will be allocated to the same arm.

5.7 Intervention and Control Arms

After the completion of recruitment and randomisation procedures and any required medical procedures according to clinical care guidelines, neonates will be allocated to receive either the intervention or standard care.

5.7.1 Delivering the intervention arm

KMC will be initiated as soon as possible following randomisation. Neonates allocated to the intervention arm will be naked except for hat and diaper. They will be secured to the exposed chest of the mother/caregiver using a KMC wrap. Prior to placing the neonate in the skin-to-skin position, a study nurse or medical officer will attach a pulse oximetry probe to the hand and a temperature probe to the torso. These procedures will take place in the admission area, prior to moving the baby to the study area. On arrival at the study area, the mother/caregiver will be seated on an adjustable bed. If required, oxygen will be provided from a cylinder or concentrator (depending on available resources at each site). Oxygen will be delivered to the neonate via nasal cannula or mask (if CPAP is required). If IV fluids are required, a bag of IV fluids will be hung and an IV cannula will be placed by a study nurse or medical officer. The study nurse or medical officer will then initiate IV fluids, with drip rate calculated according to standardised guidelines. If the mother/caregiver needs to take a short break (e.g., to shower or use the restroom), the neonate will be placed in an incubator or under a radiant heater. Every effort will be made to encourage skin-to-skin contact for 18h/day, unless otherwise clinically indicated. While we anticipate the mother will be the primary KMC provider, a family member or close friend (helper) may also provide skin-to-skin care in order to avoid disruptions. Clinical study staff at each site will counsel mothers/caregivers about KMC throughout the hospital stay, including the time of discharge. In addition, mothers who practised KMC as participants may be engaged as peer-counsellors when they return for follow-up. For each episode of skin-to-skin contact, the caregiver providing KMC (e.g., mother, father, helper) and the time of initiation and duration will be monitored and recorded in the electronic CRF (using bedside tablets).

5.7.2 Delivering the control arm

Neonates allocated to the control arm will be placed in an incubator or under a radiant heater, as per standard management at the study sites. They will wear a hat and be wrapped as per standard care. Oxygen will be provided from an oxygen cylinder or concentrator and IV fluids will be securely attached via an IV cannula with drip rate calculated, as in the intervention arm. The pulse oximeter will be placed inside the incubator or next to the radiant heater. The parent/caregiver will be able to touch the baby, if

requested, but will not provide any skin-to-skin contact until he/she meets clinical stability criteria (see Section 3.2.5), which are consistent with those used in the WHO I-KMC trial and in line with standard clinical procedures at the study sites. Once stable, the baby can transition to routine (intermittent) KMC with the parent/caregiver in a chair or bed in the study area.

5.8 Follow-up

Participants will be followed daily while admitted to the hospital (see section 6.1.2 for additional details).

At the time of discharge, all parents/caregivers will be provided with an illustrated handout on neonatal danger signs and instructed to contact the site study team or seek medical help if their baby becomes unwell. All families will be provided with phone numbers to contact the study team and a study participant ID card. Parents/caregivers will receive UgSh 20,000 (per enrolled neonate) to cover the costs of transport home and they will be able to keep the KMC wrap, so they can continue KMC at home (parents/caregivers of babies in both arms will be encouraged to continue KMC at home).

All participants will be given an appointment to attend the neonatal follow-up clinic at the respective study site on day 28-30. Transport costs (UgSh 20,000 per enrolled neonate) will also be provided to cover the costs of return transport to the study site for the follow-up visit. At this visit, repeat cUS (KNRH and JH only) and anthropometry will be performed; feeding practices and outcomes (alive, dead, readmitted) will be documented; and the WCI and Maternal Infant Responsiveness Instrument (MIRI) questionnaires will be administered to mothers.

If participants are discharged prior to day 7, additional follow-up will be arranged according to study site:

- At KNRH and JH, participants will be given an additional appointment to attend the neonatal follow-up clinic on day 7, where repeat cUS will be performed and outcomes (vital status, readmitted) will be recorded. If day 7 falls on a weekend, participants will be phoned on day 7 to ascertain outcome and the appointment will be made for the closest working day (e.g., if day 7 is Saturday, appointment on Friday; if day 7 is Sunday, appointment on Monday).
- At IH and MH, participants will be phoned on day 7 to ascertain outcome (alive, dead, readmitted) and reminded to attend the neonatal follow-up clinic appointment on day 28-30.

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

5.9 Staff Training

5.9.1 Clinical trial training workshop at MRC/UVRI before start of trial

The trial coordinator, data managers, and all site staff will attend a 5-day clinical trial training workshop at MRC/UVRI in July/August 2019. The workshop will facilitate staff becoming knowledgeable about the trial protocol and procedures; data entry and data management; other standard operating procedures; ethical conduct of research; and ensuring privacy and confidentiality.

5.9.2 Site staff training on neonatal care and clinical guidelines before start of trial

The trial coordinator and the paediatricians, medical officers, and nurses at the 4 sites will attend an additional 5-day training on neonatal care and clinical guidelines at MRC/UVRI in July/August 2019. This training will facilitate staff members' proficiency in the following areas: KMC guidelines; standardised guidelines for common neonatal conditions; Ballard gestational age scoring; pulse oximetry monitoring and recording; and counselling parents/caregivers. Training will emphasise counselling parents/caregivers about the potential for mortality at the time of enrolment, as well as counselling parents/caregivers of neonates who die or have a life-threatening event and those who witness a death. Paediatricians and medical officers at KNRH and JH will also be trained in the acquisition of cranial ultrasound (cUS) images.

5.9.3 Refresher trainings throughout trial

The trial coordinator and site paediatricians will conduct regular quality improvement activities, including refresher training on KMC and standardised guidelines, throughout the duration of the trial.

6. Study Evaluations

6.1 Clinical Evaluations

6.1.1 Evaluations during first 24 hours

All participants will receive continuous monitoring and recording of HR and SpO_2, using a pulse oximeter, for 72h post-randomisation. Continuous monitoring will continue until participants no longer require any form of respiratory support.

Axillary temperature and respiratory rate will be manually measured every 6h for the first 24h. All participants will be evaluated at least once by a study paediatrician or medical officer during the first 24h post-randomisation. Blood glucose will be measured every 6h, unless <2.6 mmol/l in which case it will be measured hourly until 2 or more consecutive readings are in normal range (2.6 – 6.9 mmol/L).

6.1.2 Evaluations from 24 hours to hospital discharge

All participants will be followed at least daily while admitted to the hospital. Unless otherwise noted, the following data will be collected and recorded in eCRFs daily from 24h through day 7 of life, then weekly on days 14, 21, and 28. If participants are discharged prior to day 7, additional follow-up will be arranged according to study site (see Section 5.8 for additional details).

a) Participants will receive monitoring of HR, SpO_2, respiratory rate, and axillary temperature every 6h until they meet stability criteria (see Section 3.2.5), after which the frequency of monitoring will transition to daily. Measurements will be recorded in eCRFs. Please refer to Section 8.1 for additional details on clinical monitoring.
b) Daily review with the following data documented:
    - Date and time of starting to receive breast milk (may be given by nasogastric tube, spoon, syringe, etc)
    - Date and time of starting breastfeeding

- Date that full breast milk feeding is established
- Daily IV fluid volumes and drip rates
- Medications administered each day, including dosage and route of administration
- Therapies administered each day, including flow rate and mode of delivery for neonates receiving oxygen
- Daily measurement of blood glucose (may be discontinued once neonate is tolerating full enteral feeds)
- Compliance with the standardised management protocol and discussion of any deviations with the site paediatrician or medical officer
- Documentation about skin-to-skin contact:
    - Date and time of skin-to-skin contact initiation
    - Duration of skin-to-skin contact/day (hours and minutes) ○ Caregiver providing skin-to-skin contact
    - Whether skin-to-skin contact is temporarily discontinued and date/time of this event
- Documentation of any change in clinical condition warranting temporary cessation of intervention and date/time of temporary cessation
- Identification of any SAE
- Documentation of any reason to suspect mother and/or baby is infected with SARS-CoV-2 (based on signs/symptoms or testing status) for babies recruited after 25 March 2020

c) Weighed on day 5, then daily until discharge (unless deemed too unstable by site study staff); weighing to be in clustered with other activities (e.g., diaper changes)
d) OFC and length will be measured weekly using study-specific equipment
e) For participants at KNRH and JH, cranial ultrasounds (cUS) will be performed on days 1, 3, and 7 of the hospitalisation, or as an outpatient if discharged before day 7 (see Section 6.1.6 for additional details)

6.1.3 Evaluations in event of clinical deterioration

Study staff at all sites will be trained to recognise signs of severe illness according to adapted possible serious bacterial infection (aPSBI) criteria (Figure 2a) and to inform study staff if a participant meets any of these criteria. The study paediatrician or medical officer (or study nurse if neither is present) will then examine the neonate as soon as possible to assess whether signs of early-onset (<72h of age) or late-onset (≥72h of age) infection (Figure 2b) are present. Neonates will be reassessed for signs of severe illness and infection during daily rounds. Where available, a blood culture will be obtained as soon as possible if a neonate meets criteria for suspected infection; however, this will not delay administration of antibiotic therapy. The site paediatrician (or medical officer, if paediatrician not present) will direct management in accordance with standardised clinical guidelines, including starting CPAP if this is local standard of care. The paediatrician or medical officer will then complete the appropriate safety monitoring documentation. Study staff will also assess if the neonate meets criteria for temporary withdrawal from the intervention arm (see Section 9). At the discretion of the study paediatrician and in line with current neonatal unit policies at each site, neonates may be referred to a higher-level facility for more specialised care; however, existing data indicate that this is an uncommon occurrence.

Figure 2a. Screening criteria for severe illness

Newborn unit staff to inform the study team as soon as possible if any of the following are present:

- Refusal to feed, feed intolerance or abdominal distension (after starting to feed)
- Lethargic (unresponsive or responsive only with tactile stimulation)
- Respiratory rate >80 breaths/min or severe chest wall in-drawing or new oxygen/CPAP requirement - Apnoea (new onset and/or persistent)
- Seizures
- Axillary temperature >37.5 degrees Celsius
- Axillary temperature <35.5 degrees Celsius (after 1h of observed skin-to-skin contact, not associated with environment or with hypoglycaemia)

Figure 2b. Additional criteria for investigation of suspected early- or late-onset infection amongst neonates screened positive for signs of severe illness

Obtain blood culture if criteria for severe illness met, plus 1 of:

- Axillary temperature >37.5 degrees Celsius
- Axillary temperature <35.5 degrees Celsius (after 1h of observed skin-to-skin contact) - Jaundice
- Apnoea (new onset and/or persistent)
- Hepatomegaly
- Pallor
- Lethargy (unresponsive or responsive only with tactile stimulation)

6.1.4 Procedures at time of discharge/death

Participants will be discharged by site study staff when they meet criteria for discharge from the newborn unit. The following data will be documented on the eCRF within 24h of discharge or death.

- Date and time of discharge/death
- Cause of death if died
- Diagnoses at time of discharge/death
- Most recent weight before discharge/death
- Details of feeding at time of discharge/death
- SARS-CoV-2 signs/symptoms and testing status/results for mothers and babies recruited after 25 March 2020

At time of discharge, parents/caregivers will be provided with an illustrated handout on neonatal danger signs and instructed to contact the site study team or seek medical help if their baby becomes unwell before the day 28-30 follow-up appointment. Families will be provided with phone numbers to contact the study team and a study participant ID card.

6.1.5 Procedures at follow-up

At the 28-30-day follow-up visit, we will record:

- Breastfeeding status
- Anthropometric measures (weight, OFC, length)

- SARS-CoV-2 signs/symptoms and testing status/results for mothers and babies recruited after 25 March 2020

For participants at KNRH EH and JH, repeat cUS will be performed at the 28-30-day visit (see Section 6.1.6 for additional details). For the MIRI, trained study staff will administer a brief, validated set of questions to all mothers at the 28-30-day visit.

6.1.6 Cranial ultrasound imaging

For participants at KNRH and JH, cUS will be performed on days 1, 3, 7, and 28-30 to examine for the presence of intracerebral pathology associated with morbidity and mortality amongst preterm infants. This includes intraventricular haemmorhage, cystic degeneration, and later hydrocephalus. The study paediatrician or medical officer at the respective sites will perform cUS using a portable ultrasound machine (Sonosite Edge II). Both standard and linear probes will be used to assess for abnormalities according to a defined protocol and to include a minimum of 11 coronal and sagittal views. Images will be read by an independent expert.

6.2 Economic Evaluation

For cost data collection for households, the project, and the hospital perspectives, multiple data sources will be triangulated to arrive at best estimates. Where possible, resource use and unit costs will be collected and presented separately, although some costs, such as out-of-pocket payments for transport do not permit this. Household costs will be collected through surveys that will be conducted with a sample of the caretakers at the time of discharge and during follow-up visits.

Project costs will be collected prospectively from project accounts using an Excel-based costing tool. These will be supplemented with time sheets and key informant interviews to inform allocation of joint costs. Direct and indirect costs incurred by providers will be collected prospectively and retrospectively using key informant interviews, facility audits, direct observations, and time-use surveys. As necessary, we may supplement secondary data on costs of treating subsequent conditions with limited primary data collection in the Ugandan study hospitals. We will model costs and effects using a lifetime time horizon.

6.2.1 Evaluations at time of enrolment

For the WCI, trained study staff will administer a brief, validated set of questions to all mothers at the time of enrolment (may be delayed to within 48h of admission). Study staff will also collect socioeconomic data at this time using standardised parent interviews (see Section 5.5.3).

6.2.2 Evaluations during hospitalisation

For household costs, direct and indirect household costs will be collected prospectively using time-use and expenditure surveys and observation of families during their hospital stay. At time of discharge/death, information regarding the time period from admission to discharge will be captured using standardised parent interviews.

6.2.3 Evaluations at follow-up

At the 28-30 day follow-up appointment, trained study staff will readminister the WCI questionnaire to all mothers. In addition, they will ask questions to ensure that costs are captured for the entire neonatal period and to inquire about families' plans going forward.

6.3 Process Evaluation

The process evaluation will be conducted in accordance with the MRC guidance on process evaluation of complex interventions (65) and will integrate both quantitative and qualitative data. In-depth interviews and focus group discussions (FGD) will be undertaken with parents/caregivers, staff, and other key stakeholders as part of the qualitative evaluation to identify experiences of KMC, facilitators and barriers to implementation and complex causal pathways. An iterative approach to qualitative analysis will be used with data collected at several time points and then used to inform later explorations.

6.3.1 Understanding causal pathways for clinical effects

Understanding the causal pathways for clinical effects of the intervention (Objective 2) will be achieved by measurement of the following process outcomes, which are categorised as providing very early (within 24 hours), early (within 72 hours), or late clinical impact:

Very early impact:

- Cardio-respiratory stability within 24 hours post-randomisation
- Prevalence of hypothermia within 24 hours post-randomisation
- Hypothermia density within the first 24 hours post-randomisation
- Prevalence of hypoglycaemia within 24 hours post-randomisation

Early impact:

- Cardio-respiratory stability within 72 hours post-randomisation
- Prevalence of hypothermia within 72 hours post-randomisation
- Hypothermia density within the first 72 hours post-randomisation
- Prevalence of hypoglycaemia within 72 hours post-randomisation
- Presence and severity of IVH within 72 hours post-randomisation

Late impact:

- Presence and severity of IVH at day 7
- Proportion of neonates exclusively breastmilk feeding at discharge
- Presence of late intracerebral sequelae of prematurity (e.g., hydrocephalus, cystic degeneration) at day 28-30

6.3.2 Focus Group Discussions

To examine the barriers and facilitators to initiating KMC before stabilisation to inform uptake and sustainability (Objective 3), we will conduct FGDs with each of the following groups: 1) providers (nurses); 2) parents (intervention and control arms). Each FGD will include 4-8 participants. FGDs conducted will broadly explore barriers and enablers to implementation of KMC before stabilisation and encourage participants to collectively identify potential solutions. Based on findings from the literature (58,59,66) and our feasibility study (56), discussion topics may include perceptions about initiating KMC before stabilisation (e.g., fear of touching small babies or dislodging oxygen masks/IV lines); parent and provider experiences with clinical care and monitoring during KMC and/or incubator care; and implementation experiences in the four hospitals [e.g., staff and peer-counselling (for parents), clinical training and guidelines (for providers), and administrative support].

6.3.3 Interviews

IDIs will be conducted with a random sample of ~24-32 care givers/family members (mother, father, and grandmother) selected for from both arms of the trial to explore social and cultural factors (e.g., family/community support, faith, stigma about preterm birth) that may influence maternal coping and compliance with care recommendations. To further inform context specific evidence on the uptake and sustainability of KMC, additional IDIs will be conducted at each site with the following stakeholders: healthcare providers involved in the care of LBW babies (1 paediatrician, 1 medical officer, 2 nurses); hospital leadership (hospital director or administrator). More interviews will be conducted with national leadership (Ministry of Health/Newborn Steering Committee and Uganda Paediatric Association member) and policymakers (WHO, UNICEF and other international bodies that support maternal and child health).

IDIs with a purposive sample of ~16 parents (8 from each arm) whose babies died during the hospital stay will explore parental experiences of trauma and bereavement. The sub-sample from the intervention arm will include parents who experienced a neonatal death while performing KMC. A Ugandan interviewer, who is fluent in Luganda/Lusoga and has experience working in a hospital setting, will receive further training on how to approach sensitive issues prior to conducting any interviews.

6.3.4 Additional health systems and clinical data

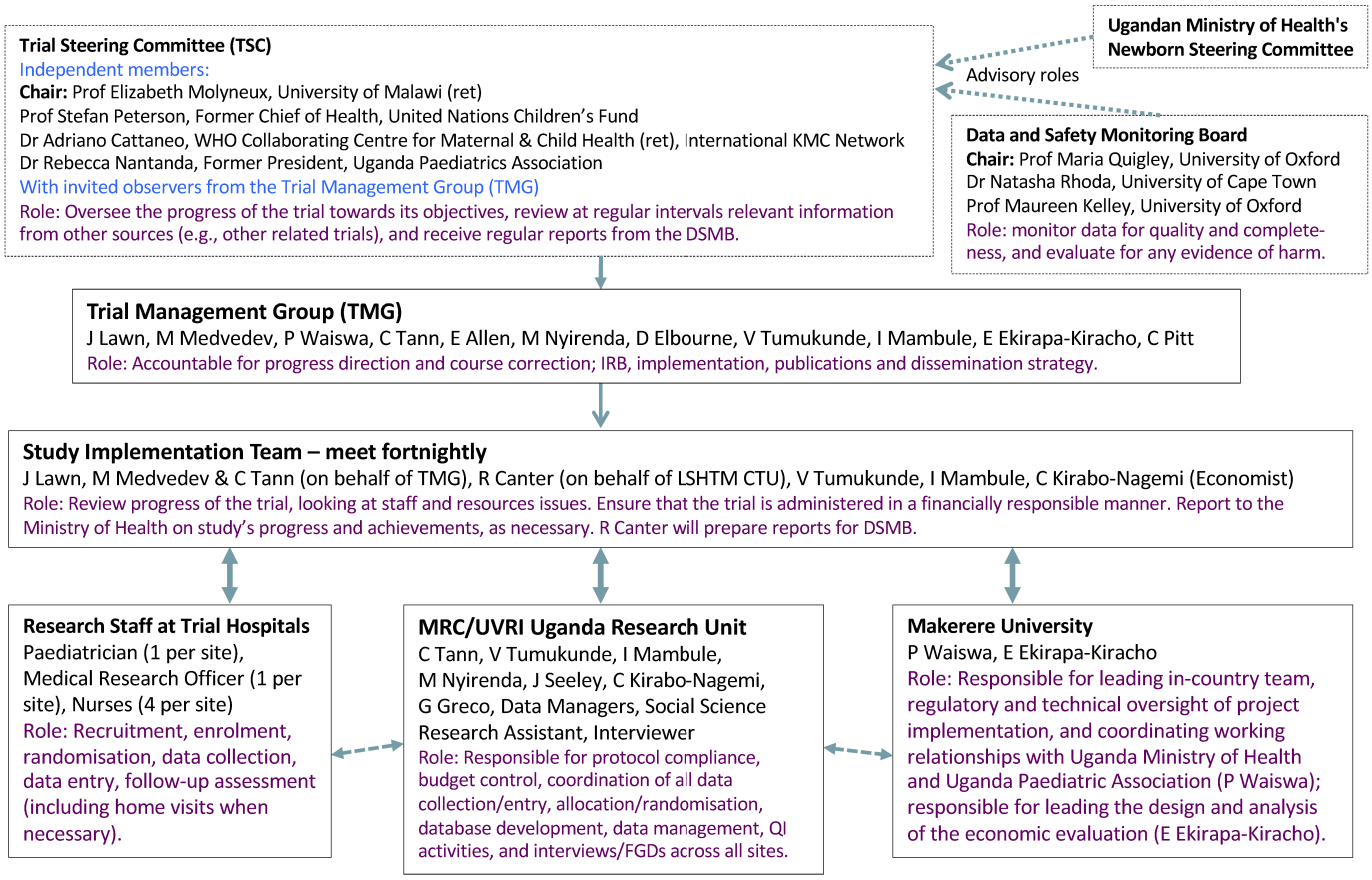
The following additional health systems and clinical data will be prospectively collected for the process evaluation:

- Admission data for all neonatal unit admissions across the five study sites to observe changes in bed capacity; referral patterns; proportion of preterm/LBW admissions; mortality rates, etc
- Triannual (every 4 months) surveys of staffing, equipment, drug/supply availability, and infrastructure at the 5 study sites
- Biannual (every 6 months) neonatal quality of care survey, including progress monitoring of KMC provision/services (Appendix E) at the five study sites
- Annual documentation of national health delivery, finances and staffing levels, including national survey of neonatal/KMC provision

7. Trial Responsibilities & Management

The OMWaNA trial is a partnership between MRC/UVRI, LSHTM and Makerere, with implementation at four Ugandan hospitals. The host institution is the MRC/UVRI and LSHTM Uganda Research Unit in Entebbe. The trial management structure is outlined in Figure 2.

Figure 2. OMWaNA Trial Management Structure



7.1 Investigator Team

Principal Investigator: **Professor Joy Lawn**

The principal investigator for the trial is Joy Lawn, Professor of Maternal, Reproductive and Child Health and Director of the MARCH Centre Director at LSHTM. She is a paediatrician and epidemiologist with >25 years of experience, including global estimates for neonatal conditions and design and evaluation of RCTs for maternal and newborn care, especially in Africa. She is an expert in newborn care research, a leader in the UN's Every Newborn Action Plan, and sits on WHO guideline review committees. Prof Lawn will provide overall trial oversight, serve as a liaison with academic partners, and lead linkage to policy uptake.

Co-principal investigators:

Melissa Medvedev (Morgan) is an Assistant Professor of Neonatology at the University of California San Francisco and a Clinical Research Fellow at LSHTM. She has been leading neonatal research in East Africa since 2006 and has worked on multiple RCTs. In Uganda, she led an RCT evaluating the feasibility of a novel paediatric mask for oxygen delivery, and she was the PI of the KMC feasibility study at JH (56). Dr Medvedev will serve as neonatal trialist, supervising the Ugandan coordination team to optimise the

protocol and reporting procedures, and she will lead the process evaluation. **Peter Waiswa** is Associate Professor of Health Policy and Planning and directs the Maternal & Newborn Centre of Excellency at Makerere University. He is a physician with a PhD in Health Systems Research and has served as PI of several neonatal RCTs in Uganda. He will provide regulatory and technical oversight, lead the in-country team, and coordinate relationships with the Ministry of Health and Uganda Paediatric Association. **Cally Tann** is an Associate Professor at LSHTM, Consultant Neonatologist at University College London, and Honorary Senior Research Associate at the MRC/UVRI and LSHTM Uganda Research Unit. She has been leading neonatal and developmental research at MRC/UVRI since 2006 and has previously lived and worked in Uganda. She is currently PI of an RCT of an early intervention programme for children at high-risk for developmental disability. Dr Tann will be the MRC/UVRI study coordinator and will work in partnership with a Ugandan coordination team. Dr Tann will provide expertise on neonatal care, physiologic data and cranial ultrasound imaging and interpretation. **Elizabeth Allen** is Professor and Head of the Department of Medical Statistics at LSHTM, specialising in the design and analysis of RCTs. She is a member of the Clinical Trials Unit management group and has extensive experience running and analysing RCTs in East Africa. Prof Allen will perform blinded analyses related to primary outcomes and give advice on other analyses. **Dr Victor Tumukunde**, is a Ugandan paediatrician with over 7 years of experience in neonatal care, including spearheading the establishment of six neonatal units at district hospitals and health centre IVs; training/ mentoring nurses to manage sick newborn babies at 78 health facilities; and coordinating a randomized controlled trial that evaluated a decision support system to empower health workers to save newborn lives in Western Uganda. He is currently coordinating the implementation of the OMWaNA trial. He will continue to provide in-country oversight of the clinical and operational activities of the trial along with the trial coordinator. **Dr Ivan Kiggundu Mambule** is a Ugandan medical doctor, currently a PhD scholar and has over 12 years of experience in clinical research in both Uganda and Malawi. He is also currently coordinating the implementation of the OMWaNA trial. He will continue to provide in-country oversight of the ethical and operational activities of the trial along with the site coordinator.

MRC/UVRI and LSHTM Uganda Research Unit investigators:

Cally Tann is a co-PI on this study and an Honorary Senior Research Associate at the MRC/UVRI and LSHTM Uganda Research Unit with experience leading RCTs at MRC/UVRI. The trial will be hosted under the Non-Communicable Diseases theme led by **Moffat Nyirenda**, a Professor of Medicine at LSHTM. Prof. Nyirenda has >25 years of experience of leading non-communicable disease research in Africa with a particular interest in the effects of early life exposures through the life course. He will serve as the senior MRC member of the Trial Management Group. **Janet Seeley** is a Professor of Anthropology and Health at LSHTM, and she directs the Social Aspects of Health Programme at MRC/UVRI. She has >30 years of experience, including 14 years in Uganda. Prof Seeley will serve as the senior advisor on the qualitative aspects of the trial and the associated process evaluation. **Christian Hansen** is the Head of Statistics at MRC/UVRI with expertise in clinical trials and maternal health. He will provide supervision and support in randomisation and data management, particularly electronic CRF data.

LSHTM investigators/collaborators:

Ruth Canter is a Trial Manager at LSHTM with a background in trial data management and statistics.

She will be responsible for producing DSMB reports, metadata creation and data sharing. **Diana Elbourne**, Professor of Healthcare Evaluation at LSHTM, is an expert in neonatal trials and ethics. She led the BRACELET study, which explored bereavement in neonatal trials (67). She will serve as senior trial and ethics advisor. **Helen Brotherton** (collaborator) is an Assistant Professor of Infectious Disease Epidemiology and a Wellcome Trust Research Training Fellow. She is the lead investigator of the eKMC trial hosted at MRC Gambia. Her research interests are in management of small and sick newborns, nosocomial infections, clinical trials and implementation of quality improvement measures.

Economic evaluation

Elizabeth Ekirapa-Kiracho is a Senior Lecturer in Health Policy and Planning at Makerere, where she focuses on maternal and neonatal health systems. She is a physician with a PhD in Health Economics. Dr Ekirapa-Kiracho will lead the economic evaluation. **Kenneth R. Katumba** is a Ugandan health economist with an MPH, who conducts a range of health economics research, including evaluating the cost and cost-effectiveness of health interventions at MRC/UVRI. Together they will design the evaluation and be responsible for data collection, analysis, and interpretation. He will conduct the economic evaluation under the guidance of Dr Ekirapa-Kiracho. **Catherine Pitt** is Assistant Professor of Health Economics at LSHTM. For >10 years, she has worked on economic evaluations in RCTs of maternal/child health interventions in Africa. She will contribute expertise in model design, data collection, and analysis. Dr **Giulia Greco** is a health economist at LSHTM, visiting Lecturer at Makerere University, and Honorary Senior Scientist at MRC/UVRI. She will lead the women's well-being assessment in partnership with Dr Ekirapa-Kiracho, Mr Katumba, and Ms Pitt.

7.2 Study Team and Infrastructure at Trial Sites

Members of the study team at each site will include 1 study paediatrician/co-investigator (20% effort), 1 study medical officer (full-time), 4 study nurses (full-time), and 1 nurse counsellor (full-time). Study paediatricians will oversee clinical decisions, supervise site staff, and ensure reporting procedures are followed (with support from the trial coordinator). Study medical officers will perform screening, recruitment, and randomisation/allocation procedures. Study nurses will assist with screening and recruitment procedures, collect and record clinical data in eCRFs, and conduct follow-up assessments, including home visits as needed. Nurse counsellors will counsel parents of seriously ill infants. In addition, local newborn unit nurses at each site will receive a stipend to assist with clinical care and data collection/entry.

Substantial expansion of neonatal care capacity and infrastructure has been embedded within the OMWaNA trial. Each hospital has a neonatal unit currently taking referrals from their respective region/district and each led by the paediatrician. The level of equipment in these government facilities differs but all have: warming areas (incubators and/or overhead radiant heaters), oxygen supply (either piped or through concentrators and cylinders), and standard operating procedures for the management of neonates including respiratory distress, apnoea, infection/ sepsis, seizures, hypothermia, and hypoglycaemia (referred to here as 'standard of care'). In addition to the government services available, substantial additional infrastructure will be added to all neonatal units to accommodate the trial. This includes improved facility building infrastructure with all study hospital neonatal care units being restructured to ensure adequate facilities for screening, recruitment and randomisation of infants and facilitation of care of non-trial participants. Site remodelling will include expansion of KMC areas within the neonatal units to ensure that all small and sick newborns, whether in KMC or not, can be cared for

acutely within the neonatal units. Site expansion includes an office for clinical staff and bathrooms and toilets for mothers attending to their babies in the neonatal care unit. All plans include fully functioning sinks in all clinical areas to provide an optimal environment for infection control.

In addition to improved building infrastructure, each unit will be supported with additional staffing and equipment. At each site, a minimum of four additional neonatal research nurses and one Medical Officer will be recruited in partnership with the neonatal Paediatrician and Neonatal Nurse In-Charge at each unit. These will be integrated within the existing staff of the neonatal units and will provide some continuity despite the staff rotations that are common in these government hospitals. Each site will also be supported by the provision of: 6 pulse oximeters (Masimo Rad-8 with neonatal sensors); 1 oxygen concentrator; 2 thermometers;1 glucose meter and glucose strips; 1 ventilation bag and mask (neonatal size); 1 neonatal weighing scale (Seca 385); 1 neonatal measuring mat (Seca 210); 2-3 paediatric stethoscopes; and a minimum of 4 adjustable KMC beds. In addition, KMC wraps will be provided to support practice in each unit. CPAP will be provided by the duty paediatrician where this is standard of care.

All participating units will receive a comprehensive training programme in neonatal care developed from established UNICEF and WHO protocols including care of the small and sick newborn, feeding and resuscitation. This includes training of neonatal resuscitation (Helping Babies Breathe) and the provision of equipment including neonatal bag and masks and resuscitation mannikins. See sections 5.9.2 “Site staff training on neonatal care and clinical guidelines before start of trial” and 5.9.3 “Refresher trainings throughout trial” for details. Continuous on-the-job support and mentorship will be provided by the resident paediatrician and site co-ordinator, a Ugandan paediatrician with wide experience in newborn care (see below for additional details) specialising in care of the preterm infants.

7.3 Trial Steering Committee

The Trial Steering Committee (TSC) will approve the main study protocol and any amendments, monitor, and supervise the trial towards its interim and overall objectives, review relevant information from other sources, consider the recommendations of the Data and Safety Monitoring Board (DSMB), and resolve problems brought by the trial coordinating centre. The TSC will meet every 6 months, with those not in the UK joining by teleconference.

Chair: Prof Elizabeth Molyneux, College of Medicine, Blantyre, Malawi

Members:

- Dr Rebecca Nantanda, President, Uganda Paediatric Association, Kampala
- Prof Stefan Peterson, Chief of Health, UNICEF, New York
- Dr Adriano Cattaneo, International Network in Kangaroo Mother Care, WHO Collaborating Centre for Maternal & Child Health (retired), Trieste, Italy

8. Safety and Monitoring

Safety oversight will be the responsibility of the investigators led by the PI, and the DSMB.

8.1 Monitoring of Study Participants

The minimum clinical monitoring schedule is shown in Table 2. In order to assess the validity of axillary temperature measurements, temperature will be continuously recorded during the first 24h post-randomisation using Grant Instruments YL-T11 temperature loggers in approximately 5% of neonates in each arm of the trial.

Table 2. Clinical Monitoring Schedule

Every 6 hours in unstable neonates in both intervention and control arms		**Daily in stable neonates in both intervention and control arms**	
Measurement	***Method***	***Measurement***	***Method***
Heart rate (continuous monitoring during first 72h post-randomisation)	Pulse oximeter	Heart rate	Pulse oximeter
Axillary temperature	Clinical thermometer	Axillary temperature	Clinical thermometer
Respiratory rate	Observe and count breaths for 1 minute	Respiratory rate	Observe and count breaths for 1 minute
Oxygen saturation (continuous monitoring during first 72h postrandomisation)	Pulse oximeter	Oxygen saturation	Pulse oximeter
Respiratory distress	Observe for chest indrawing, nasal flaring, and grunting	Respiratory distress	Observe for chest indrawing, nasal flaring, and grunting
Blood glucose (every 6h during first 24h, then daily while advancing enteral feeds)	Glucometer and blood glucose test strips		

Alarms on pulse oximeters will be set to detect bradycardia (HR <100 bpm) or hypoxaemia (SpO_2 <88%), so these neonates can be assessed by a study nurse and followed more closely. Clinically significant episodes of apnoea and/or bradycardia, which necessitate initiation of bag-mask ventilation, will be recorded as serious adverse events (SAE). See Section 6.1.3 for further details on evaluations to be completed in the event of clinical deterioration.

8.2 Adverse Events & Assessment of Causality

Adverse event (AE) terminology is outlined in Table 3. Guidelines for assessing the relationship of the intervention to the SAE are outlined in Table 4.

Table 3. Serious Adverse Events Terminology

Term	Definition
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death
	• is life-threatening • requires prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • requires intervention to prevent permanent impairment or damage
Suspected and Unexpected Serious Adverse Reaction (SUSAR)	These are the reactions that are serious (as defined above) but not expected AND considered to be related to the intervention. This definition captures the important events that are attributed to the intervention but do not follow known pattern of response.

Table 4. Guidelines for assessing the relationship of an intervention to an Adverse event

0	No Relationship	No temporal relationship to intervention ***and*** alternate aetiology (clinical state, environmental or other interventions); ***and*** does not follow known pattern of response to intervention
1	Unlikely	Unlikely temporal relationship to intervention ***and*** *a*lternate aetiology likely (clinical state, environmental or other interventions) ***and*** *d*oes not follow known typical or plausible pattern of response to intervention.
2	Possible	Reasonable temporal relationship to intervention; ***or*** event not readily produced by clinical state, environmental or other interventions; ***or s***imilar pattern of response to that seen with other interventions
3	Probable	Reasonable temporal relationship to intervention; ***and*** event not readily produced by clinical state, environment, or other interventions ***or*** known pattern of response seen with other interventions
4	Definite	Reasonable temporal relationship to intervention; ***and*** event not readily produced by clinical state, environment, or other interventions; ***and*** known pattern of response seen with other interventions

8.3 Emergency Procedures

In the event of an abnormal clinical or laboratory finding by study staff, the site paediatrician (or medical officer if paediatrician is not present) will direct management in accordance with standardised clinical guidelines. The site paediatrician or medical officer will then complete the appropriate safety monitoring documentation. See Section 6.1.3 for further details on evaluations to be completed in the event of clinical deterioration.

Providers (medical research officers and nurses) will inform the relevant site paediatrician/coinvestigator of any serious adverse event (SAE) or death occurring from the time of randomisation until the date of hospital discharge within 24 hours. The site co-investigators will notify the Trial Coordinator, who will ensure appropriate reporting procedures are followed (see Section 8.6 for further details).

8.4 Follow-up of Adverse Events

Serious Adverse Events will be followed up by the site paediatrician co-investigator until their resolution or stabilisation or until causality is determined to be unrelated to trial interventions. The outcome will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal

8.5 Assessment of Causes of Death

An endpoint review committee, comprising two individuals experienced in paediatric care in subSaharan Africa, will review all clinical, laboratory and radiological information for neonates who die during the trial to determine the causes of death that will be used in the final analysis. The endpoint review committee will remain blinded to the randomised allocations.

8.6 Reporting of SAEs & SUSARS

Information for the SAE forms will be collected as part of routine outcome data collection by the research team. The Data and Safety Monitoring Board (DSMB) will receive a summary of SAEs after 1 month of recruitment, then move to three- or six-monthly; the DSMB will decide the frequency following the first report. The DSMB will note these and, unless there is a special cause of concern, will consider them as part of the planned DSMB meetings which will discuss interim analyses. All SAEs will also be reported to the Sponsor and ethical review committees (MRC/UVRI and LSHTM) as part of their respective annual progress and safety report.

In addition, if any other serious *but unexpected* adverse event occurs, which might be related to a trial intervention, a written SAE report should be submitted to the ethical review committees (MRC/UVRI and LSHTM) within 48 hours of the investigators becoming aware of the event with a follow-up report provided within a further five working days. This expedited reporting will be limited to those outcomes not already listed as primary or secondary outcomes, yet which might reasonably occur as a consequence of the trial intervention.

It may be necessary to take appropriate urgent safety measures to protect participants from any immediate hazard to their health and safety. These measures will be taken immediately. It is not necessary to wait for ethical approval before implementing the safety measure; however, both ethical review committees and the Sponsor will be informed in writing within three working days by submitting a substantial amendment.

8.7 Data and Safety Monitoring Board

A Data Safety and Monitoring Board (DSMB) will oversee the overall integrity of the study, its safety and its continued relevance and ability to answer the primary objective.

The DSMB will meet approximately yearly during the study.

Chair: Prof Maria Quigley, Professor of Statistical Epidemiology, National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK

Members:

- Dr Natasha Rhoda, Consultant Neonatologist, Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa
- Dr Maureen Kelley, Professor of Bioethics, Nuffield Department of Population Health, University of Oxford, Oxford, UK

8.8 Stopping Criteria

The DSMB will regularly monitor all data to consider any potential harm to participants. Formal rules for stopping due to harm will be discussed with the DSMB at their first meeting.

8.9 Interim Analyses

An interim analysis will be performed on the primary outcome when approximately half of neonates have been randomised (around 1 year into the trial). An earlier interim analysis may be carried out if requested by the DSMB. The DSMB will have access to all data. An independent statistician will perform the interim analysis, blinded to treatment allocation, and report to the DSMB. The Chair of the DSMB may request additional meetings/analyses, as he or she feels necessary. In the light of these data and other evidence from relevant studies, the DSMB will inform the TSC if in their view:

i. It is evident that no clear outcome will be obtained with the current trial design.

ii. They have a major ethical or safety concern.

iii. It is evident that the intervention is clearly superior and continuing the trial would be unethical to those in the control arm.

9. Discontinuation Criteria

9.1 Criteria for stopping the intervention

Those neonates under close monitoring who meet any of the following criteria at any point during enrolment will be temporarily withdrawn from the intervention and kept in an open warmer or an incubator based on the discretion of the on-duty study paediatrician:

Stopping criteria:

Severely unstable for >10 minutes if:

- SpO_2 <88% in oxygen

AND ≥1 of:

- Respiratory rate <20 or > 100 breaths/min
- Apnoea requiring bag-mask ventilation
- HR <100 or >200 bpm

Any other condition which precludes continuous skin-to-skin contact:

a. Severe jaundice requiring immediate management
b. Severe anaemia requiring blood transfusion
c. Active seizures
d. Severe abdominal distension
e. Omphalitis or infection of the umbilical cord
f. Apnoea requiring bag-valve-mask ventilation
g. Widespread skin infection of baby or caregiver providing skin-to-skin contact
h. Mother or caregiver not available or willing to do continuous skin-to-skin contact

9.2 Criteria for restarting intervention

If a neonate is temporarily withdrawn for any of the above reasons, the intervention can be restarted once all the following criteria are met:

- No longer fill the stopping criteria
- No apnoea requiring bag-mask ventilation for 24h
- Not on phototherapy
- No seizures for 24 hours
- No abdominal distension
- Mother or caregiver available and willing to do skin-to-skin contact
- No healthcare worker concerns about clinical condition

10. Sample Size and Analysis Plan

10.1 Sample Size

Surveillance data collected on admissions to the JH neonatal unit between January and December 2016 (Perinatal Audit Data from Uganda Paediatric Association) suggest that the mortality rate in the control arm will be at least 25% across the four sites. The most recent Cochrane review and a metaanalysis demonstrated large mortality reductions among stable neonates (RR 0.60 and 0.64 respectively) (2,3), and the RCT in Ethiopia published a RR for mortality amongst neonates before stabilisation of 0.57 (4). Assuming a conservative control mortality rate of 25% across the 4 hospitals in our study, 1750 neonates (875 per arm) would enable us to detect a relative difference between arms of 22.4% (5.6% absolute difference) with 80% power and a significance level of 5%. If the control mortality rate were in fact as low as 18%, we would still be able to detect a relative difference of 27% (absolute difference of 4.8%). We plan to recruit 2188 neonates (1094 per arm) in order to allow for 10% withdrawal due to clinical deteriorations and consent withdrawal, and 10% dilution due to

noncompliance and loss to follow-up. This sample size would enable us to detect absolute reductions of 6.3% and 5.4% from control rates of 25% and 18%, respectively, with 90% power. Results from the feasibility study suggest that ≥400 eligible neonates are admitted to JH per year. Preliminary data suggest ~500 eligible neonates each are admitted to IH and EH per year and ~800 eligible neonates are admitted to MH per year. Recruitment will take place over 24 months, leading to an eligible population of ~4400 neonates. Thus, we have applied a conservative recruitment rate of ~50% to achieve the target sample of 2188. The admissions audit data from our feasibility study suggest that a higher recruitment rate should be achievable. Recruitment will continue until the target sample is reached, up to a maximum of 27 months, which includes a 3-month buffer period in case recruitment is delayed or slower than expected.

10.2 Analysis Plan for the Trial

10.2.1 Summary of baseline data and flow of patients

Baseline characteristics of enrolled neonates will be summarized by treatment arm. Descriptive statistics for continuous variables will include mean, SD, median, range, and number of observations. Categorical variables will be summarized as counts and proportions. Screening, enrolment, reasons for non-enrolment, randomisation, and loss to follow up will be detailed in a CONSORT diagram (68).

10.2.2 Primary and secondary outcome analyses

The primary and secondary outcome analyses will be carried out on all neonates as randomised ('intention to treat'). Analysis will follow a pre-specified analysis plan approved by the TSC and DSMB prior to unblinding the study database. The criterion for statistical significance at the final analysis will be $P<0.05$. The rate of loss to follow up will be reported. We will report risk ratios for mortality seven days after enrolment (primary outcome) and 28 days after enrolment (secondary outcome) for intervention versus control with associated 95% confidence intervals. Secondary outcomes: time from intervention/control procedures starting to death and length of hospital stay, will be analysed using Kaplan-Meier plots and the hazard ratios with accompanying 95% CI calculated using Cox proportional hazards regression. All other secondary outcomes will be analysed using appropriate regression models accounting for the nature of the distribution of the outcome and results will be presented as appropriate effect sizes with a measure of precision (95% confidence intervals). Both unadjusted analyses and analyses adjusted for stratification factors will be carried out. Additional exploratory analyses will control for any baseline measures that appear to be imbalanced between arms.

10.2.3 Subgroup and adjusted analyses

Subgroup analyses are planned to explore between-group difference in the impact of KMC compared to standard of care on mortality, by GA (<28, 28-32, or >32 weeks), birthweight (<1000, 1000-1499, or ≥1500g), hospital site, and level of predicted mortality risk based on the NMR-2000 score [high (≤16), medium (17-22), low (≥23)]. A paediatrician or medical research officer will conduct a Ballard examination to determine GA (27). GA is an important predictor of newborn survival. In settings with specialised neonatal care without intensive care, such as the five recruitment sites, neonatal mortality rates are 86% in neonates born at <28 weeks and 41% in neonates born at 28 to 31 weeks (51). The NMR-2000 is a simplified score to predict in-hospital mortality among neonates ≤2000g, which has been validated in the UK and The Gambia (69). NMR-2000 uses data on three parameters (birthweight, SpO_2 at admission, highest level of respiratory support at any point within 24 hours of birth), which are already being collected on enrolled neonates.

Further exploratory analyses will be carried out to explore the association between mortality and time of initiation (<12, 12-<24, or ≥24 hours), and continuity of KMC (median hours per day: <6, 6-<12, 12-<18, or 18-24 hours).

10.2.4 Definition of analysis population related to protocol non-adherence

As described above, intention to treat analyses will be conducted on the primary and secondary outcomes. All neonates will be included, regardless of protocol adherence, to prevent the effects of attrition bias.
We will also report results of per protocol analyses and complier average causal effects to account for children for whom major protocol violations were recorded such as those relating to non-compliance with the study treatments.

10.3 Analysis Plan for Economic Data

To model DALYs and costs over a lifetime time horizon in accordance with reference case specifications, we will firstly calculate the costs and discounted years of life lost (YLLs) due to neonatal deaths within the neonatal period measured in the trial. Secondly, for neonates who survive beyond 1 month, we will develop a Markov model to estimate the costs and discounted years of life with disability (YLDs) lost and additional YLLs from premature mortality attributable to health conditions associated with prematurity and LBW. If there is a difference between trial arms in rates of breastfeeding, the impact on morbidity and mortality of the differential rates of breastfeeding will also be modelled. The model structure and parameters will be informed by existing literature (47) and by consultation with clinical experts, including the PI and other members of the trial team. If neither intervention exhibits strict dominance (i.e., is less costly and more effective), we will model incremental cost per neonatal death averted and per DALY averted, in line with reference case specifications. Deterministic and probabilistic sensitivity analyses will be conducted to assess the robustness of results to uncertainty and heterogeneity.

We will examine budget impact by using the incremental financial costs incurred in the trial context to project how these costs may vary at scale and which budgets would bear the incremental costs or reap the cost savings. For example, we envisage additional cost burden at the national level to train on KMC, which is likely to require donor support, but potential cost savings at the hospital level in reduced equipment and maintenance costs. We will compare cost burden with existing budgets, where relevant, and engage with policy makers to understand affordability at different levels.

Equity will be explored by examining variation in incremental costs to households and in health and well-being outcomes across socioeconomic groups.

10.4 Analysis Plan for Qualitative Data

Interview/FGD data will be transcribed and, where necessary, translated into English. Data will be analysed using the thematic content approach (70,71). Using this approach, data analysis will consist of four steps: (1) familiarisation; (2) identifying codes and themes; (3) developing a coding scheme and applying it to all of the data; (4) organising codes and themes. Dr Medvedev and the Ugandan interviewer will read all interview/FGD transcripts and develop the preliminary coding schemes together. Dr Medvedev and the interviewer will individually code 10% of transcripts from each portion of the qualitative evaluation. Any discrepancies will be discussed and resolved to develop the final coding frameworks. Dr Medvedev will code all remaining transcripts. New themes that emerge outside the

coding framework will also be included in the analysis (72,73). Qualitative manuscripts will follow the consolidated criteria for reporting qualitative research (74).

11. Quality Control and Quality Assurance

The PI will ensure that staff involved with the trial are:

- Properly qualified to assume responsibility for conduct of the study
- Willing to comply with GCP and applicable regulations
- Prepared for audits and monitoring
- Able to recruit study participants in sufficient numbers and on time
- Well informed about the protocol and their study responsibilities The site clinical leads will ensure that their respective sites have:
- Sufficient human and material resources to sustain routine standards of care
- Staff who are well informed about the protocol, the IP, and their study responsibilities and are fully trained in the relevant SOPs

11.1 External Monitoring

The study will be monitored by the Clinical Studies Support Office at MRC/UVRI, who will develop a risk-based monitoring plan for the study. The monitoring team comprises of trial coordinators and trial managers from the various trials currently running within the unit. To achieve independence during the monitoring, one dedicated study monitor, independent of the study team, will be assigned to monitor this study. The monitor's role is part of the quality system and will oversee the progress of the trial and ensure that the trial is conducted and data are handled in accordance with trial SOPs, the protocol, Good Clinical Practice (GCP) and applicable ethical and regulatory requirements.

11.2 Internal Monitoring

Internal monitoring will be conducted by the central study team (PIs and trial coordinator) as a continuous process through direct communication with the site paediatricians and medical research officers via telephone or email and physical site visits.

11.3 Audits and Inspections

The study may be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

11.4 Indemnity

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies that apply to this trial.

12. Data Management

At the hospitals, trial data will be electronically entered on tablets into a GCP-compliant, offline, trialspecific mobile application [Research Electronic Data Capture (RedCap), Nashville, TN, USA]. REDCap has a built-in audit trail that automatically logs activity including log-ins, user rights, data entry/modification, data export, and running reports. Only the PIs, the trial coordinator, and the data managers will have access to this database.

12.1 Data Transmission and Editing

Data from tablets, which will be partially anonymised (participant names excluded), will be synced once daily over a secure 3G connection with a web-based RedCap database. The system will be centrally hosted at the MRC/UVRI data centre. Anonymised pulse oximeter and temperature logger recordings (linked by participant ID) will be captured in MS Excel files, securely transmitted to MRC/UVRI, and entered into the trial database. Data including pulse oximeter / temperature recordings, will be transferred to Stata for analysis. Cranial ultrasound images will be stored in OsiriX Dicom imaging software and interpreted blind to allocation and clinical details. Logs linking parent/guardian names and residence location will be stored separately on a password-protected computer, with a hard copy stored in locked cabinets in secure rooms at the sites.

We will utilize the inbuilt access management and audit trail functions of REDCap to track changes to the data, implement role assignment and restrict unauthorized access to study data.

12.2 Data Discrepancy Inquiries

REDCap has a built-in audit trail that automatically logs activity, including log-ins, user rights, data entry/modification, data export, and running reports. Only the PIs, the trial coordinator, and the data managers will have access to this database.

Internally developed Stata verification/cleaning do-files will be run by data managers to identify data that are missing, inconsistent, or out-of-range. The trial coordinator will perform clinical quality checks to identify potential errors not captured in the automated verification process.

Query resolution: The trial coordinator or data managers will raise queries through the RedCap query management system and assign it to a member of the study team at the respective site, who will respond to it. Only after a satisfactory response is given will the query be closed. Pending queries will be allowed up to 2 days if the patient is still hospitalised or 5 days if patient has been discharged.

12.3 Qualitative Data

To ensure a standardized approach is used for FGDs/interviews at all sites, interviewers will be issued a FGD or interview guide and a pre-specified list of target respondents. FGD/interview data will be collected, with consent of participants, through audio-recording and field notes. Transcripts will be linked by study ID to other forms of data collected for the study. Master records with ID numbers and identifying information will be stored separately.

12.4 Security and Backup of Data

All data will be stored in institutional servers at MRC/UVRI during the study. A complete backup of the database onto external hard drives will be performed twice per month. Hard drives will be stored at MRC/UVRI and retained for a minimum of three years after publication of the research. Audio files will be digitally recorded and securely stored on a computer as password protected files until transcription and verification are completed. At the end of the study, all study documents with names or addresses will be destroyed.

Data from the web-based RedCap database will be downloaded and stored on institutional servers at LSHTM for access by the PIs and independent statistician for analysis and preparation of reports for the DSMB, respectively. These secure, password-protected servers are only accessible within the LSHTM network from specified user accounts. Access is controlled by Firewall policy based on the host address

and application. Activity on LSHTM servers are fully audited recording both login details and file system access. Access will be limited to essential research personnel.

No names or other direct identifiers will appear in typed documents, transcripts, or recordings. FGD/IDI transcripts will be pseudo-anonymised with unique confidential codes and identification codes will be kept in a separate secure location. The electronic master-log linking participant-identifying information will be stored on a password-protected computer and a hard copy master-log stored in a locked filing cabinet under the custody of the trial coordinator. Consent forms will be stored in locked cabinets in secure rooms at the sites.

12.5 Study Status Reports

The data manager at MRC/UVRI will prepare weekly email reports with information on missing and incongruent data. The trial coordinator will review these reports and inform the data manager regarding any necessary corrections.

12.6 Access to Data

Data from the web-based RedCap database will be downloaded and stored on institutional servers at LSHTM for access by the PIs and independent statistician for analysis and preparation of reports for the DSMB, respectively. These secure, password-protected servers are only accessible within the LSHTM network from specified user accounts. Access is controlled by Firewall policy based on the host address and application. Activity on LSHTM servers is fully audited recording both login details and file system access. Access will be limited to essential research personnel.

12.7 Responsibilities

The PIs, trial coordinator, data advisor, and data managers will be responsible for data management, quality assurance, and data security. Ms Canter (UK data manager) will be responsible for metadata creation and data sharing. Policies of the LSHTM Research and Governance Office will govern study-wide data management and metadata creation activities, and policies of LSHTM Information Technology will govern data security.

13. End of Trial and Archiving

At the termination of planned recruitment, the Trial Coordinating Centre will contact the site by telephone or email in order to terminate all patient recruitment as quickly as possible. If the study is terminated prematurely by the Steering Committee, the site will be informed immediately. When all recruited patients have been followed until hospital discharge or death, a declaration of the end of trial form will be sent to the relevant IRBs. The following documents: original consent forms, data forms, trial related documents and correspondence, will be archived in the Site File and kept for at least five years. At the end of the analysis and reporting phase, the Trial Master Files at the Trial Coordinating Centre will be archived for 15 years.

14. Ethical Considerations

14.1 Ethical approvals and general considerations on human subject participation

Approval will be obtained from the UVRI Research Ethics Committee, the Uganda National Council for Science and Technology, and LSHTM. Annual progress reports will be submitted to the IRBs within 30

days of the anniversary date on which the favourable opinion was given until the trial is declared ended. The PI will notify the IRBs of the end of the study. Substantial amendments that require review by IRB will not be implemented until the IRB grants a favourable opinion for the study. All correspondence with the IRB will be retained in the Investigator Site File.

14.2 Rationale for inclusion of vulnerable groups

14.2.1 Rationale for Neonates

Our study aims to investigate KMC, initiated before stabilisation, amongst neonates ≤2000g. As such, we are obligated to study neonates. These small neonates are at high risk, and in these low-resource Ugandan hospitals without intensive care, standard care using incubators, often shared with other neonates, exposes them to significant risks (e.g., infection). KMC has been shown to reduce many of these risks and could have major mortality gain. WHO and others have stated that determining the effect of KMC initiated prior to stabilisation is an important and justifiable research question, notwithstanding these risks. Our team includes neonatal trialists, including an expert in ethical issues in neonatal trials, and we will address concerns through careful monitoring of neonates and DSMB monitoring.

14.2.2 Rationale for children ≥15 years of age (who are parents of included neonates)

According to the Uganda National Council of Science and Technology, “emancipated minors are individuals below the age of majority who are pregnant, married, have a child or cater for their own livelihood,” and “mature and emancipated minors may independently provide informed consent to participate in research” (75). Uganda has a high rate of teenage pregnancy. According to the Uganda Demographic Health Survey (UDHS 2011), 24% of women are already mothers or pregnant with their first child before the age of 19, and 39% of women aged 20 to 49 gave birth by age 18 (2).

14.3 Evaluation of risks and benefits

14.3.1 Potential risks or benefits of standard care in Uganda

Incubators are the standard alternative to KMC for maintaining normothermia in preterm and low birthweight neonates. In resource-limited facilities such as the four trial hospitals, it is common for several neonates to share one incubator or radiant heater. In this trial, neonates randomised to the control group will receive standard care. Risks associated with standard care with an incubator or radiant heater include hypothermia (40,76); hyperthermia (77); nosocomial infections, related to lack of effective cleaning standards (78–80); and cross-infection from other neonates when incubators are shared, a common practice in low-resource facilities. Failure of incubators/heaters to properly regulate temperature may be related to malfunction (e.g., over- or under-heating) (77,80–83), loss of electrical supply (51), ignorance of how to regulate set-points (77), as well as environmental factors (81). In lowresource hospitals, where there may be few nurses and doctors available, neonates nursed in incubators/heaters may not be monitored well, and illness or serious events (e.g., apnoea) may not be detected in time. Such events may be detected more rapidly when neonates are in the KMC position with their mother (or another caregiver). Further, due to high purchase cost and poor routine maintenance practices, hospitals in low-resource settings commonly face shortages of functional incubators (50–52,84).

14.3.2 Potential risks or benefits of KMC in Uganda

Evidence from meta-analyses: The most recent Cochrane review found that KMC is associated with decreased mortality [RR 0.60, 95% CI 0.39-0.92 (8 trials)], sepsis [RR 0.35, 95% CI 0.22-0.54 (5 trials)], and hypothermia [RR 0.28, 95% CI 0.16-0.49 (9 trials)] at discharge or 40-41 weeks postmenstrual age, compared to standard care amongst stable neonates ≤2000g (20). A meta-analysis showed that KMC is also associated with decreased mortality at latest follow-up among infants <2000g [RR 0.64, 95% CI 0.46-0.89 (15 studies)], sepsis [RR 0.53, 95% CI 0.34-0.83 (8 studies), hypothermia [RR 0.22; 95% CI 0.12-0.41 (9 studies), and hypoglycaemia [RR 0.12; 95% CI 0.05-0.32 (2 studies)] (21).

***Evidence from high- and middle-income countries*:** Most studies of KMC have suggested enhanced autonomic stability (39,40,85,86) and decreased frequency of apnoea and desaturation (31,33,36,87), as well as improved breastfeeding, weight gain and lower rate of infections (20). One German study of 22 spontaneously breathing neonates less than 32 weeks' gestation found that the combined frequency of bradycardia and hypoxaemia increased from 1.5/hour before to 2.8/hour during skin-to-skin contact episodes (P<0.05) (88). In a follow-up study, they showed that the total rate of bradycardia and desaturation was higher during skin-to-skin contact (median 3.0 per hour) than incubator care following skin-to-skin contact (with ambient temperature elevated by 1°C) (1.7 per hour, P<0.02) (89).

Numerous studies have reported improved thermal control with KMC (28,32–34,36,41,42,76,90), whilst one found no difference in the incidence of hypothermia (31). In a study of 34 ventilated neonates (mechanical or nasal continuous positive airway pressure ventilation) in the Netherlands (91), neonates at gestational ages between 25^{+0}-26^{+6} weeks had a mean skin temperature decrease of 1.1% during KMC (P= 0.0001) and 1.4% after KMC (P=0.0002). Neonates between 27^{+0}-29^{+6} weeks gestation had a decrease of 0.5% during KMC, which was not statistically significant, and a decrease of 0.8% after KMC (P=0.012). Importantly, heart rate, respiratory rate, and SpO2 remained within safe ranges at all times in both groups. They concluded that KMC is safe for ventilated neonates under 30 weeks' gestation "as long as skin temperature is monitored and extra warmth is provided if necessary" (91). These studies underline the importance of adequate monitoring of preterm neonates during KMC.

***Evidence from low-income countries*:** Only two RCTs have evaluated the effect of KMC on mortality at discharge or term-equivalence (40-41 weeks postmenstrual age) in low-income countries. The only RCT for mortality effect in neonates before stabilisation, which was conducted in Ethiopia, reported major mortality reduction in neonates in the KMC group compared to those in the radiant warmer group (RR 0.57, p<0.05) (23); however, it had important methodological deficiencies. An RCT amongst 285 stabilised neonates in Ethiopia, Indonesia, and Mexico found no difference in mortality, but did report decreased hypothermia and increased weight gain in the KMC arm (29). A more recent RCT of 126 stable neonates in Nepal also found that neonates in the KMC arm had decreased hypothermia and increased weight gain (28). An RCT in Madagascar, which compared KMC initiated within 24 hours to KMC initiated 48-72 hours post-birth in a sample of 73 stable neonates, found no difference in incidence of mortality at 28 days, hypothermia, apnoea, or severe infection (38).

14.3.3 Overall assessment of clinical risk

Preterm birth is associated with a significant risk of mortality, particularly in settings without neonatal intensive care. This study will enrol neonates before stabilisation, according to the eligibility criteria above. Based on the available evidence, and a comparison of the risks and benefits of KMC and standard care in a low-resource setting, KMC is unlikely to present any greater risk to participants

meeting eligibility criteria than conventional care, however, to ensure clinical safety neonates will have continuous monitoring of vital function (heart rate, oxygen saturations).

14.4 Sensitisation

Antenatal, maternity and neonatal staff at each study site will be sensitised to the study (see page 26)

14.5 Informed Consent

Obtaining informed consent for this RCT may be challenging given the involvement of sick neonates (30); the fact that KMC needs to be started as soon as possible after birth; the fact that some women are not literate; and the fact that some women may be too ill, especially within the first 24 hours, to provide consent or participate. Parental stress is compounded by the fact that complications may be unexpected, especially in low-resource settings, where knowledge of preterm birth is generally low. To help address these issues, this RCT will utilise the continuous consent approach (31), which involves giving parents/caregivers information at multiple time points both before and after recruitment (32). Studies have found that the validity of consent improves when discussion continues after recruitment (31,33). The continuous consent process was utilised in the Total Body Hypothermia (TOBY) trial, which investigated the use of whole-body cooling for neonates with evidence of perinatal asphyxia (92). The continuous consent approach has three main elements (92), all occurring after delivery, which are outlined here in the context of the OMWaNA trial:

1. While a neonate is assessed for eligibility (upon admission to the newborn unit, or the following morning if admission occurs outside normal working hours), parents will be given preliminary information about the trial.
2. If the neonate is eligible, a comprehensive information sheet will be provided and further discussion will take place, including assessment of whether the parents are willing and able to participate. At this point, parents will be asked for their written consent and neonates will be randomised.
3. During the intervention period, the site paediatrician or medical officer will meet with parents to ensure that they understand the trial procedures and wish to continue to participate in the trial. It will be made clear that they may withdraw their baby from the trial at any time.

Information about the trial will be made available to women attending the antenatal clinic and labour ward. If a mother is unavailable or too ill to provide consent, informed consent will be obtained from the father. Site staff will receive training on obtaining consent, including legal and ethical constraints governing the process (34). Information sheets (Appendix A) will be available in English, Luganda, and Lusoga (local dialects). Oral and written explanations will be provided at the same time to improve parent/caregiver understanding and ensure information is accessible to those with lower levels of literacy (34). Medical officers or study nurses will obtain consent prior to enrolment. Consent will be documented with a thumbprint if a parent/caregiver cannot write. During the informed consent process, parents will be reminded that they have a right to refuse participation (or their neonate's participation), with no consequences. They also have the right to withdraw from the study at any point with no consequences.

14.6 Confidentiality

All enrolled neonates will be assigned a trial number. All reports, data collection, and administrative forms will be identified with the trial number only to maintain confidentiality. All study-related materials will be stored securely at the study site. All information on enrolled neonates will be stored in locked file

cabinets in areas with limited access. All records that contain personal identifiers will be stored separately from study records identified by trial number. The local database will be password-secured.

14.7 Care of families whose newborn dies or who has life-threatening events

Training of site staff will emphasise counselling parents/caregivers about the potential for mortality at the time of enrolment as well as counselling parents/caregivers of neonates who die or have lifethreatening events and those who witness a death. Each site will have one full-time study nurse counsellor to counsel parents of seriously ill infants. In addition, women who have practised KMC may be engaged as peer-counsellors. After the trial ends, findings will be shared with families and thoughtfully adapted for those affected by a death (67).

14.8 Transport Reimbursement to Participating Mothers

Transport costs (UgSh 20,000 per enrolled newborn) will be provided for participating women on discharge to cover the costs of transport home at the end of the study. Mothers will be able to keep the KMC wrap provided for babies enrolled in the study, so they can continue KMC at home. Transport costs (UgSh 20,000 per enrolled newborn) will also be provided to cover the costs of return transport to the hospital for the 28-day follow-up visit. The reimbursement will be provided to women when they come to the hospital for the follow-up visit.

15. Involvement of Participants and the Public

15.1 Incorporation of Feasibility Study Findings into Trial Design

The feasibility study showed that the majority of parents and healthcare providers felt confident to use KMC in neonates prior to stabilisation. Challenges included lack of beds/space, and lack of staff and devices to monitor neonates. Stakeholders believed that KMC practice, and neonatal care more generally, could be improved through staff and peer-counselling, more beds, and improved availability of clinical monitoring devices. This feedback has been incorporated into our trial design as follows:

- Clinical staff at the four study sites will counsel parents/caregivers throughout the hospitalisation of their newborn.
- KMC peer-counselling programmes will be established, enlisting mothers who practiced KMC when they return for follow-up, at the four study sites.
- Hospital administrators at the four study sites will be engaged regarding KMC guidelines.
- Adjustable beds will be provided to improve adherence with the recommended duration of KMC in the intervention arm.
- Increased space is being organised for the JH and MH newborn units to provide room for KMC beds/chairs and existing incubators.
- Masimo Rad-8® pulse oximeters and digital thermometers will be provided to the four study sites to enable improved monitoring of HR, SpO_2, and temperature.

15.2 Local Advisory Board

We will engage a local advisory board including district health authorities, local community leaders, academics (MRC/UVRI, Makerere University), national health organisations (Uganda Paediatric Association), and policymakers (Newborn Steering Committee of Ugandan Ministry of Health). The

advisory board will be led by Prof Waiswa (Co-PI), who has previously engaged similar advisory boards for other newborn studies in Uganda. This advisory board will meet quarterly to provide guidance on local issues related to trial implementation and implications for local households and communities.

15.3 Workshops and Qualitative Evaluations

The process evaluation will include two half-day workshops in Uganda after the first 6 months of recruitment. The first, focused on local communities, will include district health authorities, community leaders, paediatricians, nurses, and parents. During the trial, we will conduct FGDs with healthcare providers, parents, and hospital administrators to explore barriers and enablers to implementation of KMC before stabilisation, and to help inform context-specific evidence on the uptake and sustainability of KMC. Throughout the trial, IDIs with mothers will explore social and cultural factors that may influence maternal coping and compliance with care recommendations. IDIs with parents whose babies died during the hospital stay will explore their experiences of trauma and bereavement.

15.4 Sharing of Study Findings with Participating Families

After the study ends, findings will be shared with families, and thoughtfully adapted for those affected by a death (62).

16. Declaration of Interests

The PI, Co-PI, co-investigators, supervisors, and collaborators have no financial relationships to disclose or conflicts of interest to resolve. The proposed research does not use technology or materials subject to IP protection, nor will it lead to commercially exploitable results. Further, it is not subject to agreements with commercial, academic or other organisations.

17. Potential Limitations and Anticipated Challenges

Among neonates in the control group, non-compliance with allocation (e.g., parents demanding early KMC) is a potential issue; however, this has not been reported in other trials (20). Compliance in both arms, particularly the KMC arm, could be affected by parents witnessing a death (e.g., in the KMC position). Some babies will die regardless of the trial arm to which they are randomised. Preterm neonates can die quickly, even in settings with intensive care, and such deaths are a recognised impediment to KMC practice (93). Stigma regarding preterm birth is common in Uganda, but has not impeded KMC practice for stable babies (94). Notably, the two deaths in the feasibility study did not negatively impact recruitment or discourage other parents from practicing KMC. Clinical study staff at each site will counsel parents about the potential for mortality at the time of enrolment as well as counsel parents of neonates who die and those who witness a death.

In the intervention arm, adherence to the target duration of KMC (≥18 hours/day) may be difficult to achieve. Among five RCTs that promoted continuous KMC, three reported durations of ≥20 hours per day (29,30,43) and two did not report duration (23,38). Among 10 RCTs evaluating intermittent KMC, one reported mean/median duration of 17 hours/day (42), five reported 10-14 hours/day (32,33,35,36,41), and three reported <10 hours/day (28,34,37). A comprehensive approach will be used to improve adherence. An illustrated KMC handout will be provided to mothers at the time of enrolment. Clinical site staff will counsel mothers throughout the hospital stay, including the time of discharge. Studies have noted the importance of staff training and counselling for KMC (95,96). We will establish KMC peer-counselling programmes at each hospital, enlisting mothers who practiced KMC as

participants when they return for follow-up. Peer counselling will address many maternal concerns and may help facilitate longer durations of KMC. A related RCT demonstrated the efficacy of peercounselling in promoting breastfeeding amongst hospitalised neonates (97). We will also engage hospital administrators about KMC guidelines. Adjustable beds and KMC wraps will be provided, as these have been shown to improve adherence (98). Increased space is being organised for the JH and MH newborn units for KMC beds/chairs and existing incubators.

18. Significance of the Proposed Work

Globally, there are an estimated 2.5 million neonatal deaths each year (15), among which >80% occur in neonates who are small at birth, due to being preterm and/or SGA (16). Major mortality reductions could be achieved by improving care of small neonates in low-resource settings (16–18). WHO guidelines recommend KMC for "routine care of newborns weighing ≤2000g… initiated as soon as newborns are clinically stable" (8), where stability has been defined as vital functions (breathing, circulation) not requiring "continuous medical support and monitoring," and not being "subject to rapid and unexpected deterioration" (3). However, estimates suggest that ≥75% of neonatal deaths occur before stabilisation in settings without intensive care (16,17,22). Further, over three-quarters of neonates in sub-Saharan Africa and south Asia lack access to intensive care (99). The only RCT of KMC in neonates before stabilisation with mortality outcomes was conducted in Ethiopia (123 neonates ≤2000g). It reported a 43% reduction in mortality (RR 0.57); yet, 66% of deaths and the major difference between arms occurred within 12 hours of birth (18,23). In addition, this RCT excluded >50% of eligible neonates, did not utilise allocation concealment, and had an apparent group imbalance at baseline (favouring KMC) (23), compromising robustness (18,100). Thus, the effect of KMC initiated before stabilisation in hospitals without neonatal intensive care remains a research priority, still not being addressed, and a well-designed RCT is warranted to examine mortality impact in non-intensive care settings (18).

19. Publication and Dissemination Plan

19.1 Dissemination Policy

We will aim to publish the trial protocol and results as well as the economic, qualitative, and process evaluations in prestigious, peer-reviewed academic journals with open access, guided by a dissemination plan. The main trial results will be launched with a press release from MRC/UVRI, LSHTM's MARCH Centre, and Makerere University, with social media in Uganda, UK and globally. This material would also lend itself to film for public engagement, and our group have a track record of major media uptake globally and also specifically on Ugandan TV. We will aim to present the study results at international meetings such as the International Paediatric Association and Paediatric Academic Societies, and to key audiences (WHO, UNICEF, International KMC Network) and funders (including MRC, Wellcome Trust, DFID, Gates Foundation, CIFF, ELMA). All manuscripts resulting from the trial will adhere to the Consort Guidelines (68).

19.2 Plans to Grant Public Access to Protocol

Per the recommendation set forth in the Ottawa statement (101), the full protocol will be made publicly available through clinicaltrials.gov or through publication in a scientific journal.

20. Timeframe

The timeframe for the proposed work is set out in the following figure (Figure 3). **Figure**

3. OMWaNA Study Timeline

21. Acknowledgments

The formative work investigating the feasibility of KMC initiated before stabilisation was funded by the UCSF Preterm Birth Initiative and the Thrasher Research Fund. This protocol has been developed in collaboration with the eKMC trial investigators led by Dr Helen Brotherton, and the experiences of the eKMC trial have substantially informed the development of this protocol.

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Appendices

Appendix A: Patient information sheet and informed consent form (parents/guardians)

Appendix B: Information sheet and informed consent form for qualitative evaluations (health care workers and key stakeholders)

Appendix C: Ballard score for estimating gestational age

Appendix D: Case report form

Appendix E: KMC Progress Monitoring Tool for Health Faciities

Appendix F: Investigators' CVs