Trial protocol

Early Kangaroo Mother Care in Gambian Hospitalised Unstable Neonates (eKMC)

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CLINICAL TRIAL PROTOCOL

A randomised controlled trial of early continuous skin-to-skin contact versus standard care on survival of hospitalised unstable neonates <2000g in The Gambia

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The clinical trial will be carried out in accordance with: the study protocol; the tripartite harmonized ICH Guideline for Good Clinical Practice 1996; the MRC Guidelines for the Management of Global Health Trials 2017; UK Research Governance Framework for Health and Social Care 2005; the UK Data Protection Act 1998 and MRC Good Research Practice: Principles and Guidelines 2012.

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Protocol amendment(s)

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List of abbreviations

AE	Adverse event
AMR	Antimicrobial resistant
aSCRIP	Adjusted Stability of cardio-respiratory in preterm infants
BVM	Bag-valve-mask ventilation
CLSI	Clinical and Laboratory Standards Institute
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous positive airway pressure
Cm	Centimetres
CSF	Cerebro-spinal fluid
DSMB	Data safety monitoring committee
eCRF	Electronic case report form
EC	Ethics committee
EFSTH	Edward Francis Small Teaching Hospital
ESBL-KP	Extended Spectrum Beta-lactamase producing Klebsiella pneumoniae
GCP	Good clinical practice
GNB	Gram-Negative Bacilli
HAI	Hospital acquired infection
HIC	High income country
HIV	Human Immunodeficiency virus
ICH	International Conference on Harmonization
ID	Identification
IV	Intravenous
KMC	Kangaroo Mother Care
LBW	Low Birth Weight
LMIC	Low-middle income country
LOS	Late onset sepsis
LSHTM	London School of Hygiene and Tropical Medicine
MDR	Multi-Drug Resistant
MRC	Medical Research Council
MRCG	MRC Unit The Gambia
NMR	Neonatal mortality rate
OFC	Occipito-frontal circumference
PCR	Polymerase Chain Reaction
PI	Principal Investigator
RDS	Respiratory distress syndrome
RV	Recto-vaginal

SAE	Serious adverse event
SCC	Scientific Coordinating Committee
SOP	Standard operating procedure
SPO_2	Peripheral capillary oxygen saturation
SDG	Sustainable development goal
SSP	Study specific protocol
TMF	Trial Master File (regulatory file)
WHO	World Health Organization

DEFINITIONS

Adverse event:	"Any unfavourable and unintended sign, symptom, laboratory finding or disease which was absent at baseline, or if present at baseline, appears to worsen AND is temporally associated with the participants involvement in the research"
Apnoea:	No spontaneous breathing for either 20 seconds, or less than 20 seconds and associated with colour change; hypoxia (SPO2 <88%) or bradycardia (heart rate <100 bpm)
Low birth weight:	Birth weight 1500 - 2499g
Very low birth weight	Birth weight 1000 - 1499g
Extremely low birth weight:	Birth weight less than 1000g
Neonatal period:	Period from birth to 28 days
Early neonatal period:	0 – 6 days after birth
Late neonatal period:	7 – 28 days after birth
Neonatal mortality rate:	Number of neonates dying before 28 days of age, per 1000 live births per year
Preterm birth:	Birth at <37+0 completed weeks gestation
Extreme preterm:	Birth at <28+0 weeks gestation
Very preterm:	Birth at 28+1 – 31+6 weeks gestation
Moderate-late preterm:	Birth at 32+0 – 36+6 weeks gestation
Serious Adverse event:	Any untoward medical occurrence which:[1] a) Results in death b) Is life threatening (Neonatal Near Death) c) Requires prolonged hospitalisation d) Results in persistent or significant disability / incapacity

Eligibility:

Stable clinical condition**:**	SPO_2 ≥88% in room air for 10 minutes AND all of: ✓ Respiratory rate 20 – 60 breaths/min ✓ No apnoeic episodes requiring bag-valve-mask ventilation ✓ No severe chest indrawing
Mild instability:	A. SPO_2 ≥88% **in air** for >5 minutes AND all of: ✓ Respiratory rate 60 – 100 breaths/min ✓ No apnoeic episodes requiring bag-valve-mask ventilation ✓ No severe chest indrawing OR B. SPO_2 ≥88% **in oxygen** for >5 minutes AND none of: ✓ Respiratory rate 60 – 100 breaths/min ✓ Severe chest in-drawing ✓ Apnoeic episodes requiring bag-valve-mask ventilation
Moderate instability:	A. SPO_2 ≥88% in oxygen for >5 minutes AND ≥1 of:Respiratory rate >60 breaths/min ✓ Respiratory rate <20 b/min ✓ Severe chest in-drawing

- ✓ Apnoea requiring bag-valve-mask ventilation
- ✓ HR <100 or >200 beats/min

B. SPO_2 <88% in oxygen for >5 minutes AND none of:
- ✓ Respiratory rate <20 or >100 breaths/min
- ✓ Severe chest in-drawing
- ✓ Apnoea requiring bag-valve-mask ventilation
- ✓ Heart rate <100 or >200 beats/min
- ✓ CPAP

Severe instability: Either:

A. SPO_2<88% in oxygen for >5 minutes

AND ≥1 of the following:
- ✓ Respiratory rate <20 or > 100 breaths/min
- ✓ Severe chest in-drawing
- ✓ Apnoea needing bag-valve-mask ventilation
- ✓ HR <100 or >200 beats/min

OR

B. CPAP is required on clinical grounds as per Standardised Preterm Management Protocol

Summary of stability definitions:

	Stable	**Mild**		**Moderate**			**Severe**	
In oxygen	No	No	Yes	Yes			Yes	CPAP**
SPO2*	≥88%	≥88%	≥88%	≥88%	≥88%	<88%	<88%	
	AND all of:	**AND all of:**	**And none of:**	**AND ≥ 1 of:**	**AND ≥ 1 of:**	**AND none of:**	**AND ≥1 of:**	
Respiratory rate*	20 - 60	60 - 100		>100 or <20				
Severe chest in-drawing	No	No		Yes				
Apnoea needing BVM ventilation	No	No		Yes				
Heart rate*				<100 or >200				

*Oxygen saturation, heart rate and respiratory rate classified according to those present for ≥5 out of 10 minutes observation. If the values are present for 5/10 minutes classify the baby in the less severe category. E.g. If oxygen saturation is in range ≥88% for 5 minutes and <88% for 5 minutes the baby is classed as having oxygen saturation of ≥88%

**If CPAP is required baby is classed as severely unstable, regardless of oxygen saturation. The decision to start CPAP is made according to the Standardised Preterm Management Protocol.

Major congenital malformation: A malformation which 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

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Interventions:

Kangaroo mother care:	Package of care consisting of prolonged skin to skin contact between baby and caregiver (usually mother); promotion of exclusive breast milk feeding and early hospital discharge with close follow up
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
Early continuous skin-to-skin contact	Skin-to-skin contact between baby and mother/caregiver for at least 18h/day and starting within 24h of birth

Outcomes

All-cause mortality:	Death of a neonate due to any reason within a defined time period
Suspected late onset infection:	New onset of any 1 of the following at > 72h of age: Pallor; Lethargy; Jaundice; Apnoea; Hepatomegaly[2]
Confirmed late onset infection:	New onset of any 1 of the following at > 72h of age: Pallor; Lethargy; Jaundice; Apnoea; Hepatomegaly[2] AND blood or CSF culture positive for known neonatal pathogen
Hypoglycaemia:	Blood sugar level < 2.6 mmol/l, as measured by bedside testing
Hypothermia:	Auxillary temperature less than the normal range (36.5°C – 37.5 °C)[3]
Mild hypothermia:	36.0 °C – 36.4 °C
Moderate hypothermia:	32.0 °C – 35.9 °C
Severe hypothermia:	<32.0 °C
Hypothermia density:	Proportion of time temperature <36.5 °C during a defined time period
Duration of admission:	Time from hospital admission to discharge

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Protocol summary

Title:	A randomised controlled trial of early continuous skin-to-skin contact versus standard care on survival of hospitalised unstable neonates <2000g in The Gambia
Alias :	eKMC
Population:	392 hospitalised mild-moderately unstable neonates weighing <2000g and aged 1 – 24h
Number of participants:	392 newborns (ratio 1:1)
Number of Sites:	1 recruitment site
Location of Sites (including satellite sites):	Neonatal unit at Edward Francis Small Teaching Hospital, Banjul, The Gambia
Trial Duration:	
- Clinical Phase:	Recruitment over period of 24 months
- Whole trial:	Whole trial: 25 months
Duration for Participants:	Neonates will be followed up from enrolment within 24h after birth to 28 days Mothers/caregivers will be consented for paired biological swab samples at/shortly after admission
Description of intervention:	Kangaroo mother care is a package of care for preterm/low birth weight (LBW) neonates consisting of: prolonged skin to skin contact; promotion of early & exclusive breast milk feeding; early hospital discharge with close follow up. Intervention arm: Subjects will receive the continuous skin-to-skin contact aspect of KMC as soon as possible within 24h after admission Control arm: Subjects will be managed in incubators or radiant heaters, as per standard care, with skin-to-skin contact (KMC) started when clinically stable at >24h of admission
Objectives:	Objective 1.To assess the effect of early continuous skin-to-skin contact on survival of hospitalised, mild-moderately unstable neonates weighing <2000g Objective 2. To assess the effect of early continuous skin-to-skin contact on other important clinical outcomes for hospitalised, mild-moderately unstable neonates weighing <2000g Objective 3. To assess the safety of early continuous skin-to-skin contact in the hospital management of mild-moderately unstable neonates <2000g

Objective 4. To explore early (thermal control, cardio-respiratory stability) and late (infection prevention control, gastro-intestinal stability) mechanistic pathways for the beneficial effects of early continuous skin-to-skin contact compared to standard care in hospitalised, mild-moderately unstable neonates weighing <2000g.

Outcomes:

Primary outcome:
All-cause mortality at 28d

Secondary outcomes:

1. Time from intervention/control procedures starting to death (days & hrs)
2. Mean cardio-respiratory stability at 24h of intervention (aSCRIP score)
3. Prevalence of hypothermia (T<36.5^{o}C) at 24h of intervention
4. Mean daily weight gain (g/day) at 28d
5. Proportion of infants exclusively breastfeeding at discharge
6. Mean duration of hospital admission (days & hours)
7. Incidence of clinically suspected infection after 3 days and by 28 days or latest follow up
8. Prevalence of neonatal intestinal carriage of ESBL-Klebsiella pneumoniae at 28d

Description of Study Design:

This individually randomised, controlled, superiority trial will compare 2 parallel groups of hospitalised mild-moderately unstable preterm/LBW neonates receiving either early continuous skin-to-skin contact (<24h since admission) (intervention group) or standard care (control group) (ratio 1:1). Randomisation will be in random permuted blocks of varying sizes with allocation of twins to same arm. The intervention will be un-blinded to participants and researchers with blinding of outcomes where possible. Interventions will be maintained until hospital discharge and encouraged post-discharge with routine follow-up at 28 days. If participants become unwell whilst receiving the intervention and fulfil criteria for stopping, they will revert to standard care and re-commence skin-to-skin contact when stability criteria are met, in keeping with the control arm. Intention to treat analysis will be used.

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Background information

Burden of neonatal & preterm/low-birth weight mortality
Global neonatal mortality remains unacceptably high with the highest neonatal mortality rate (NMR) occurring in West and Central Africa region at 31/1000 live births[4] and a large disparity in newborn survival between resource limited and resource rich regions.[5] In contrast to impressive recent reductions in the global under-5 mortality rate, the NMR is declining at a much slower rate[5] and neonatal deaths now account for 46% of all U5 deaths.[4] The neonatal mortality rate (NMR) in The Gambia reduced from 50/1000 live births in 1990 to 28/1000 live births in 2016[4] but remains significantly higher than the Sustainable Development Goal (SDG) target of reducing NMR to <12/1000 live-births by 2030.

15 million babies are born preterm every year[6] and complications of prematurity are the single largest direct cause of under-five mortality world-wide, causing 1.1 million deaths per year[7] with a high burden of morbidity in survivors. In addition, low-birth weight (LBW) is an independent risk factor for neonatal mortality with the highest risk of death in those born preterm and small for gestational age (SGA).[8] An estimated 14% of all Gambian babies are born preterm[9] and complications of preterm birth is the most common cause of death at the main neonatal referral centre in The Gambia.[10] If SDG targets are to be met, a focus on feasible and effective hospital based management strategies for preterm babies in early neonatal period is critical to target the estimated 83% of prematurity related deaths occurring during this period.[11]

Kangaroo mother care is an evidence-based intervention for preterm/LBW hospitalised babies
Kangaroo mother care (KMC) is recommended as standard care for all *stable*, hospitalised babies <2000g.[12] It was developed in Colombia four decades ago and since adopted in both HIC and LMIC as an adjunct to incubator care. KMC is a complex intervention with the key component prolonged, continuous skin-to-skin contact between the nearly naked baby and mother's chest. The full definition, as described by Charpak et al, also includes promotion of early and exclusive breast-milk feeding, early discharge and close follow-up.[13] Although other caregivers can provide skin-to-skin contact, a key aspect of KMC is the stimulation of maternal breast milk production and subsequent effects on feeding and growth.
Skin-to-skin contact and KMC are often used as synonyms in the literature, but for the purposes of this trial, early continuous skin-to-skin contact is considered the intervention under study.

Clinical benefits of KMC include reduced risk of: nosocomial infection; hypothermia, hypoglycaemia, severe infection and illness with moderate evidence of increased weight, length and head circumference gain and improved exclusive breast feeding at discharge, term and latest follow-up in *stable* neonates weighing less than 2000g.[14,15,16] KMC also reduces duration of hospitalisation[14, 15] and hospital re-admission[15] which benefits both neonate, mother and health care system.
According to several systematic reviews, continuous KMC (>18h/day) reduces mortality by 36 - 51% compared to conventional incubator care.[14,15,16] The most recent Cochrane review (2016) reported a 40% reduced risk of mortality at discharge or 40-41 weeks postmenstrual age (RR 0.60, CI 0.39-0.92; 8 trials, 1736 infants) and latest follow-up (RR 0.67, CI 0.48-0.85)[14]. However, this mortality effect is for "stable" neonates <2000g and there is an evidence gap for the mortality-effect of KMC in unstable babies within 24h after birth, when preterm/LBW babies undergo a physiological transition from in-utero to ex-utero life and are at greatest risk of mortality or near death events such as apnoea, hypoxia and bradycardia.

Early, continuous skin-to-skin contact in unstable babies
Early continuous skin-skin contact immediately after birth stabilises the newborn's cardio-respiratory system[17] but there is limited evidence for clinical and mortality effects in the unstable population. Clinical stability is variably defined in previous KMC studies with no standardised WHO definition or validated clinical model for resource limited settings. Of 20 RCTs

included in 3 systematic reviews,[14,15,16,] with mortality outcome at latest follow-up, KMC was initiated within mean or medium 4 days of age in 7 studies and only 1 studied mortality effect as the primary outcome in unstable neonates (Table 1).[18] Worku et al reported 40% reduction in mortality with early KMC in 123 neonates (22.5% vs 38%; p<0.05; RR0.59, 95% CI 0.34 – 1.03) but was underpowered with exclusion of >50% of eligible subjects, poorly defined case definitions and selective reporting of outcomes.[18] There are no other published studies of early continuous skin-to-skin contact in unstable babies in resource limited settings with adequate power to examine mortality effect.

Understanding mechanistic pathways for benefit of early continuous skin-to-skin contact

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.[19]

The key causal pathways underpinning the protective benefit of KMC are: thermal control; reduction in cortisol and stress response; cardio-respiratory stabilisation; enhanced breast milk supply and breast milk 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 early skin-to-skin contact is not fully known and this work would contribute towards understanding the physiological processes underpinning a potential benefit of early continuous skin-to-skin contact (early KMC).

Understanding how KMC reduces hospital acquired infections has not been widely researched, especially in resource limited settings where the bacterial burden and risk of nosocomial infections is high.[20] Possibilities include: reduced exposure to environmental pathogens; protective effect of maternal microbiome[15] and enhanced immunity through transfer of breast milk immune factors and/or microbiome. Late-onset infections in neonatal units of resource limited settings are predominantly due to gram-negative bacilli (GNB) and staphylococcus aureus, with GNB responsible for over 50% of all infections in hospital born neonates[20] There is no data for the effect of KMC on GNB carriage and limited evidence that KMC alters the neonatal oral microbiome with decrease in Pseudomonas and increase in Streptococcus.[21] This a unique and un-explored area of KMC research which may give insight into the reported 65% reduction in hospital acquired infection.[14]

In summary, research into the clinical effects and safety of KMC, or continuous skin-to-skin contact in *unstable* babies has been highlighted as a research priority[14] and warrants robust investigation to identify the mortality and clinical effects, safety and explore mechanisms underlying the potential protective effects of this feasible and life saving intervention.

Feasibility study to inform planning of eKMC

From April to August 2017, a prospective observational feasibility study was conducted at the study site with the aims of understanding the target population and assessing the feasibility of conducting the clinical trial. From this data and previous published audit data[10] from the study site, the clinical trial is considered feasible with an estimated 245 clinically eligible patients admitted per year. Barriers to recruitment are absence of caregiver within 24h of admission (21%), death or severe instability during screening period (23%) and consent refusal (14%). Mortality in eligible subjects at 28d is 56% (14/25) with median age at time of death 3d 2h and 71% (10/14) of all deaths occurred within the first week of admission. The feasibility study also identified key enablers and barriers to the provision of early KMC. These included maternal willingness to practice continuous KMC with good family support and the need for enhanced education of both health care workers and parents about providing early KMC alongside other medical interventions. These results will inform the sensitisation, planning and conduct of the clinical study.

References of literature and data are listed in Section 18.

1.2 Rationale

Neonatal mortality remains unacceptably high and complications of prematurity are the most common, direct, cause of death in children aged under 5y. Feasible hospital based interventions to reduce mortality in resource limited settings are urgently needed.

The hospital management of preterm/LBW babies is challenging in resource limited settings, for multiple reasons, including: lack of essential newborn care and supportive management; high patient: health care worker ratios and increased risk of hospital acquired infections. Investigation and development of feasible, low cost strategies for the management of these babies within the critical early neonatal period is a global research and public health priority.

Kangaroo mother care is an evidence based and safe intervention currently used for stable newborns <2000g with significant mortality effect. Early, continuous skin-to-skin contact used in unstable newborns has the potential to improve survival through a combination of early and late mechanistic pathways, of which thermal control, cardio-respiratory stability and infection prevention control are the most important.

It is hypothesised that early continuous skin-to-skin contact in mild-moderately unstable neonates will improve survival by:

1. *Early* onset, *early* impact, stabilisation pathways which improve thermal control, promote cardio-respiratory stabilisation and modulate the natural history of preterm complications.
2. *Early* onset, *late* impact, pathways include prevention of late-onset infection, promotion of gastro-intestinal stability through improved breast milk feeding and improved recognition of apnoeic events needing resuscitaiton.

1.3 Potential risks and benefits

KMC is known to be a safe intervention for stable newborns and has multiple, evidenced based benefits including mortality and infection reduction (section 1.1.) Although the safety profile of early continuous skin-to-skin contact in resource limited settings with low level clincial monitoring is less well established, there is evidence from resource rich neonatal intensive care settings that using skin-to-skin care alongside other medical interventions is safe and well tolerated.[22]

The potential risks to human subjects and known benefits are summarised in Section 14.3.

2 STUDY OBJECTIVES & OUTCOMES

2.1 Objectives

Objective 1. To assess the effect of early continuous skin-to-skin contact on survival of hospitalised, mild-moderately unstable neonates weighing <2000g
This will be achieved by measurement of the primary outcome of mortality at 28d and secondary outcomes of time to death..

Objective 2. To assess the effect of early continuous skin-to-skin contact on other important clinical outcomes for hospitalised, mild-moderately unstable neonates weighing <2000g

This will be achieved by measurement of the following secondary outcomes:

- Growth (weight)
- Duration of hospital admission

- Suspected late onset infection

Objective 3. To assess the safety of early continuous skin-to-skin contact in the hospital management of mild-moderately unstable neonates <2000g

This will be achieved by measurement of the following secondary outcomes:
- Cardio-respiratory stability at 24h

Objective 4. To explore causal pathways for the beneficial clinical effects of early continuous skin-to-skin contact compared to standard care in hospitalised, mild-moderately unstable neonates weighing <2000g

This will be achieved by measurement of the following secondary process outcomes:
- Time to mortality
- Cardio-respiratory stability at 24h (early pathway)
- Hypothermia (early or late pathway)
- Exclusive breastmilk feeding at discharge (late pathway)
- Prevalence of intestinal ESBL-Klebsiella pneumoniae carriage (samples to be taken and stored, pending future funding)

- In addition and also as part of objective 4, carriage swab samples, environmental samples and blood/CSF culture isolates will be stored with the intention of undertaking the following work at a future stage, once additional funding is secured:

1. Explore the effect of early skin-to-skin contact on neonatal intestinal/rectal microbiome, with comparison to maternal/caregiver microbiomes (16SrRNA)
2. Describe the molecular epidemiology of ESBL-KP isolates, including clonal diversity and antibiotic resistance profile (whole genome sequencing)
3. Compare neonatal carriage and invasive isolates with environmental isolates and maternal/caregiver carriage isolates to explore transmission of neonatal pathogens (whole genome sequencing)

2.2 Outcomes

Primary outcome:
All-cause mortality at 28d

Secondary outcomes:

1. Time from intervention/control procedures starting to death (days & hrs)
2. Mean cardio-respiratory stability at 24h of intervention (aSCRIP score)
3. Prevalence of hypothermia (T<36.5^{o}C) at 24h of intervention
4. Mean daily weight gain (g/day) at 28d
5. Proportion of infants exclusively breastfeeding at discharge
6. Mean duration of hospital admission (days & hours)
7. Incidence of clinically suspected infection after 3 days and by 28 days or latest follow up
8. Prevalence of neonatal intestinal carriage of ESBL-Klebsiella pneumoniae at 28d

3. Study design

3.1 Type of study and design

This individually randomised, controlled, superiority trial will compare 2 parallel groups of hospitalised preterm/LBW newborns receiving either early continuous skin-to-skin contact (started at 1 - 24h after birth)(intervention group) or standard care and late KMC (started at >24h) once clinically stable (control group) (ratio 1:1). The intervention will be un-blinded to participants and researchers with blinding to outcomes, where possible. Interventions will be maintained until hospital discharge and encouraged post-discharge with daily in-patient review and follow up at 28 days. If participants meet criteria of being severely unstable (definitions, page 10) whilst receiving the intervention they will revert to standard care and re-commence KMC when stability criteria are met, in accordance with current standard care (section 7). Primary analysis of primary and secondary outcomes will be on an intention to treat basis. A pragmatic study design will be used with a standardised preterm/LBW clinical management protocol based on current standard care and provided by study site staff. In-order to explore the infection prevention control mechanisms underpinning this intervention, paired maternal /caregiver swab samples will be taken at time of admission in addition to environmental swab samples.

3.2 Setting

The study will be conducted at the neonatal unit of Edward Francis Small Teaching Hospital (EFSTH), with technical and laboratory support from MRC Unit, The Gambia (MRCG).

The neonatal unit is the major referral unit in The Gambia, accepting in-born and out-born admissions. Approximately 1400 neonates are admitted annually,[10] of which 25% weigh <2000g and are aged <24h.(unpublished) The overall case fatality rate is 38% with very low birth weight (VLBW) a risk factor for mortality[10] and 58% case fatality rate in neonates weighing <1500g.[10] This is consistent with feasibility study data reporting a 28d mortality rate of 56% in neonates who would be eligible for the clinical trial. (unpublished)

Current standard care for preterm/LBW neonates includes care under incubator or radiant heaters; oxygen via concentrators; nasal CPAP; IV fluids given by burette if available; IV caffeine; IV ampicillin, gentamicin, cloxacillin, metronidazole and ceftriaxone. Continuous monitoring is not available but twice daily temperature and once daily vital signs, including oxygen saturation and blood glucose, are done routinely on critical patients. Neonates <2000g currently receive intermittent KMC for minimum 60 minutes, 4 – 5 times a day once they are stable and off oxygen. They are admitted to the KMC unit for continuous KMC when not receiving IV medications or fluids. There are unit guidelines and monitoring documents available and the study site staff have been trained in KMC theory and practices.

3.3 Randomisation and blinding procedures

3.3.1. Randomisation

Randomisation will be performed by an independent statistician with computer generated random number tables to give a random allocation of numbers in permuted blocks of varying block sizes.Stratification by admission weight categories will be used with separate random number tables if <1200g or ≥1200g. Allocation concealment will be performed with opaque, sealed envelopes labelled consecutively with the randomisation number (RN00X) and containing a piece of paper stating the randomisation number and the treatment allocation. A research clinician or nurse not connected to the study will prepare the envelopes.The envelopes will be securely kept in a cabinet at the study site office. Following the screening process and collection of baseline data, treatment allocation will take place according to the content of the sealed envelope, in consecutive order of randomisation number. Prior to opening the envelope, the date, time andunique study ID of the baby

will be written on the outside of the envelope and the envelope will be stored for later auditing. Subjects who are of twin birth and completed twin admissions will be allocated to the same arm, according to the twin that was declared eligible first. A randomisation log will be kept to ensure that the randomisation procedure is correctly followed.

3.3.2. Blinding

Due to the nature of the intervention, it is not possible to blind participants or study personnel to the intervention arm. Participants, health care providers, data collectors and investigators will be blinded to outcomes where possible and applicable, such as cardio-respiratory stability, and results of biological samples.

3.4. Description of intervention

KMC is a package of care recommended by WHO[12] as standard care for *stable* neonates <2000g and consists of: prolonged skin to skin contact between baby and caregiver; promotion of early and exclusive breast milk feeding; early hospital discharge and close follow-up. In this study, continuous skin-to-skin contact started early (1 – 24h of age) is the intervention under study. Skin-to-skin contact will be provided for as long as possible, aiming for at least 18h/day. Further details on the study procedures for both the intervention and control arms are detailed in section 5.1.2.e.

3.5 Concomitant medications/treatments

All other medicines and treatments will be prospectively recorded on the hospital medical record and electronic CRF (eCRF). They will be provided to the participant as per a standardised preterm/LBW management protocol, based on current standard care and guidelines at the study site. The protocol will include details on routine stabilisation, fluids, feeding and respiratory management; complications of prematurity/LBW (hypoglycaemia, jaundice etc); medications, investigations and discharge / transfer and follow-up criteria.

The protocol will be based on a combination of direct observation, available guidelines and will be developed in collaboration with the medical team at EFSTH. Compliance with WHO guidelines will be encouraged, where possible. Compliance to the standardised preterm/LBW management protocol will be monitored regularly through-out the study and also analysed for any significant differences in key indicators at the end of the study. Any obvious discrepancies in treatment between the two arms will be identified prospectively and actions taken to ensure that both arms receive the same medical and nursing treatment.

4 SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 Selection of participants

Participants will be selected from new admissions to the neonatal unit at EFSTH. All new admissions will be screened by weight, as performed by the hospital staff as part of routine practice. Admissions weighing less than 2000g will undergo screening for eligibility.

4.2. Eligibility of participants

The eligibility criteria are aimed at capturing the mild-moderately unstable neonate <2000g and aged 1 – 24h old. Severely unstable neonates will be excluded as it is practically challenging to provide continuous skin-to-skin contact if the baby requires frequent resuscitation and medical attention. The severely unstable neonates are also unlikely to survive the initial 24h - 48h after admission (unpublished data) as there are currently no intensive care interventions available at the study site. According to WHO recommendations[12], stable preterm/LBW babies should all receive continuous KMC as standard

care and it would not be ethical to randomise this group to receive incubator or radiant heater care when they would otherwise receive KMC.

Participants must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the trial.

4.2.1. Inclusion criteria

Neonates:

- New admission to the neonatal unit at EFSTH during the study period
- Admission weight less than 2000g
- Age 1 – 24h at time screening begins
- Alive at time of enrolment
- Singleton or completed twin birth admission
- Written informed consent provided by a parent/caregiver

Mother/caregiver:

- Paired neonate is enrolled in the study
- Is available and willing to provide continuous skin-to-skin contact
- Provides written informed consent

4.2.2 Exclusion criteria

Neonatal recruitment

- Congenital malformation which is incompatible with life or requires immediate surgical correction
- Severe jaundice needing immediate management
- Seizures
- Clinically stable as assessed over a pre-defined period of cardio-respiratory monitoring (see definitions, page 10)
- Severely unstable as assessed over a pre-defined period of cardio-respiratory monitoring (see definitions, page 10)
- Completed triplet admission
- Mother and/or neonate already enrolled into another MRCG study at time of hospital admission
- No study bed available

Neonatal rectal swabs (at all time points):

- Imperforate anus
- Gastrointestinal surgery since birth
- Diarrhoea or watery stool within 24h of swab

Neonatal skin swabs (at all time points):

- Topical antibiotic or topical steroid used on neonatal skin since birth or within preceding 7 days
- Multiple blisters, pustules, boils, abscesses, erosions or ulcers on the scalp, face, neck, arms, forearms or hands
- A single blister, pustule, boil, abscess, erosion, ulcer, scab, cut, crack or pink/hyperpigmented patch or plaque at or within 4 cm of the sampling site

Maternal recto-vaginal swab

- Known HIV infection
- Major gastro-intestinal surgery within the last 5 years
- Diarrhoea or constipation within the preceding 24h

Maternal/caregiver skin swab

- Known HIV infection
- Used topical antibiotic or steroid on skin within 4cm of sampling site in last 7d
- Generalised skin disorder (eczema, psoriasis, scabies, multiple blisters, pustules, boils or abscesses)
- A single blister, pustule, boil, abscess, erosion, ulcer, scab, cut, crack or pink/hyperpigmented patch or plaque at or within 4 cm of the sampling site

4.3 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. If a participant in the intervention arm meets the pre-defined "stopping" criteria they will temporarily stop the intervention and receive standard care until able to re-commence KMC, as per standard care (section 7). Participants are free to withdraw from the study at any time without giving a reason.

5 STUDY PROCEDURES

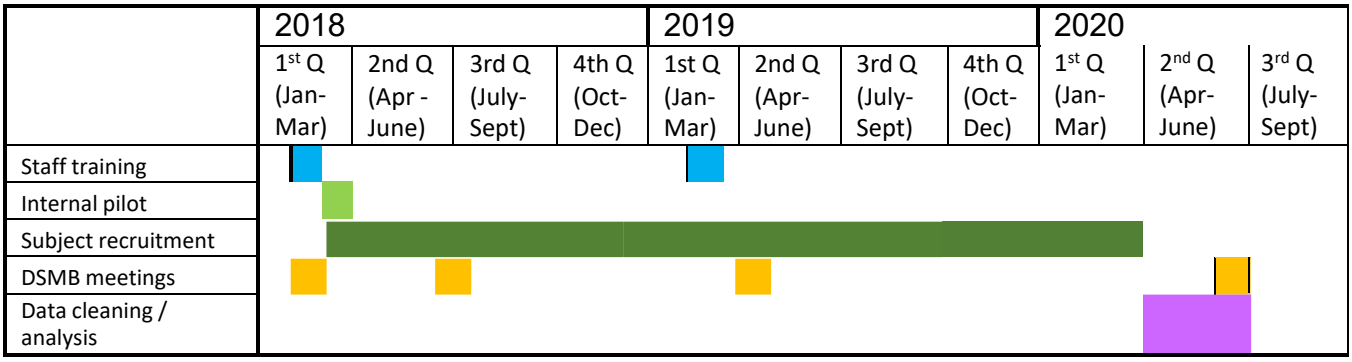
All study procedures will be conducted in accordance with ICH-GCP principles and all research personnel involved in the study will undergo ICH-GCP training. Health care workers at the study site will be trained on study objectives, overview of procedures, standardised management protocol and asked to inform study personnel of any potential participants and in the event of a clinically deterioration. Study site health workers will be paid a stipend for involvement with the study but will not perform any study related procedures.

5.1 Internal pilot

All study personnel will undergo training according to study specific procedures to ensure high quality data collection. This will take place prior to an internal pilot phase involving recruitment of 10 participants with piloting of the data collection tools and processes and trial of providing the intervention alongside other medical interventions (E.g. oxygen, IV fluids). This will enable refinement of the study procedures and documentation. If procedures are judged to be adequate and in accordance with ICH-GCP principles, the participants will be included in the sample for the overall trial.

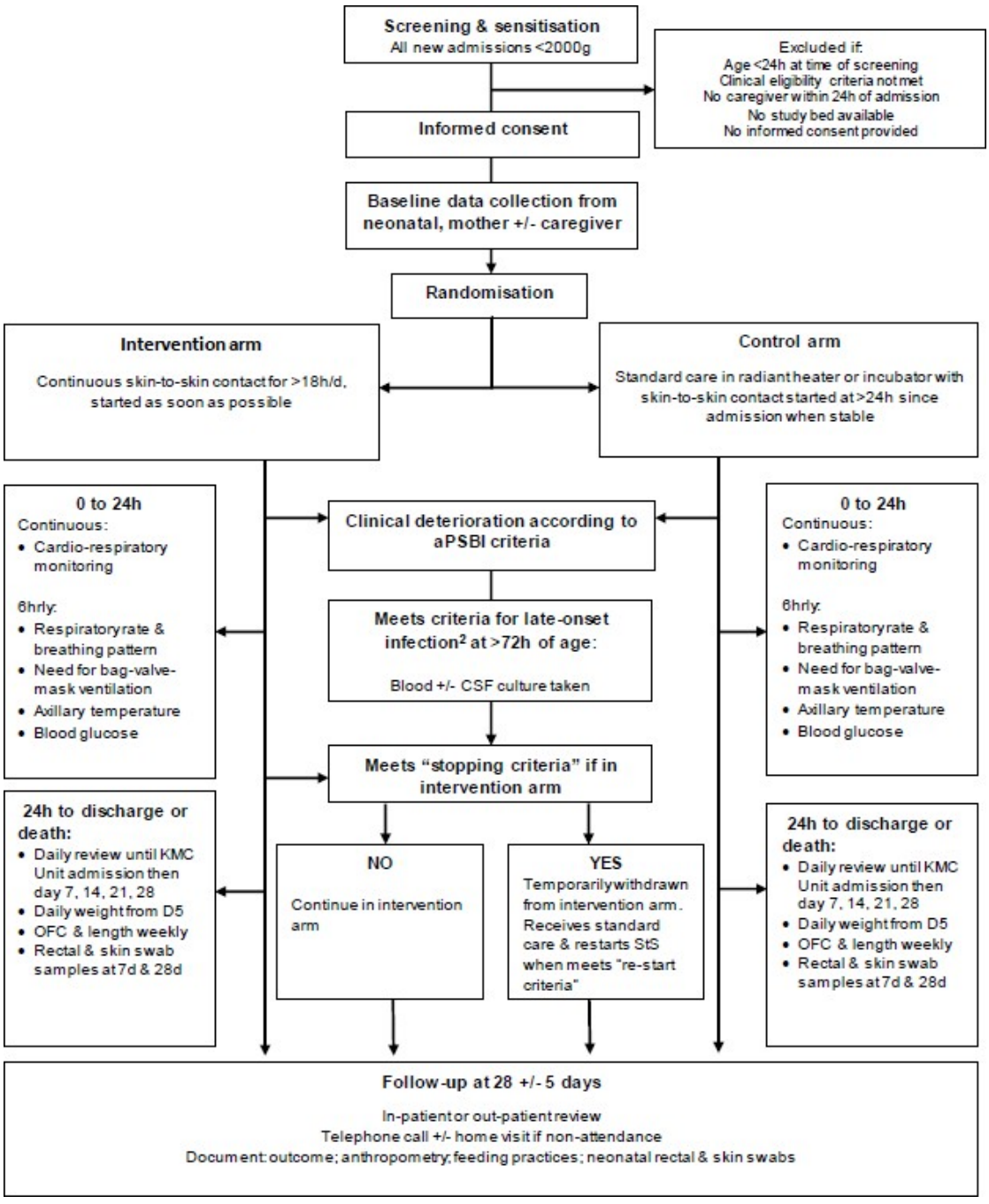
5.2 Study schedule

Figure 1. Timeline with key milestones for clinical study



Protocol #: 1

Figure 2: Study schedule with overview of study procedures



5.3 Screening

See appendix I for a summary of screening and enrolment procedures and estimated timings.

5.3.1 Screening for potential participants:
All new admissions to EFSTH neonatal unit weighing <2000g will undergo screening for potential participation by study personnel, as outlined below. An admission log will be maintained prospectively by study personnel to document all admissions to the neonatal unit during the study period. This will give information on the occupancy of the neonatal unit during the study period and the proportion of neonates undergoing screening. If available on the neonatal unit, parents / caregivers of neonates <2000g will be sensitised about the study.

5.3.2 Screening for eligibility:

- Eligibility will be assessed as soon as possible after admission and once the subject 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 MRCG research nurses with support from the Research Clinician or PI

The screening procedures will take place at the radiant heater or incubator where the neonate has been admitted by the hospital staff in the following order:

1. It will be ascertained if the mother/neonate is already enrolled in another MRCG research project, by checking the maternal hand-held record and, if so, no further screening processes will take place.
2. Neonatal age will be checked by direct questioning of caregiver/escort and/or examination of the referral letter, antenatal card or medical record.
3. If neonate is aged <24h, they will be re-weighed on the study weighing scale to ensure weight is less than 2000g and a standardised weight is obtained
4. Examination for obvious external congenital malformations, severe jaundice and seizures in addition to general examination
5. A pulse oximeter (Nonin 2500A) with neonatal probe will be attached for continuous monitoring and documentation of heart rate and oxygen saturation for initial 10 minutes.
6. Manual measurement of the respiratory rate will be performed every minute for 10 minutes. This will be combined with observation of the breathing pattern and documentation of whether bag-valve-mask ventilation is required for management of apnoea.
7. Temperature and blood glucose will be measured as part of routine care and to assist in management of the baby

It is recognised that preterm/LBW babies can have significant variations in clinical stability over the initial hours after birth and the screening process is intended to identify those neonates who either deteriorate and become severely unstable, or improve their clinical condition following admission and initial resuscitation.

At the end of the 10 minute period, if the baby meets all of the stable criteria they will be excluded and receive standard care. If criteria for mild instability are present, the subject will be recruited. If moderate or severe instability is present (definitions, page 10), continuous pulse oximetry will continue for further 2h 50 minutes (3 hours total) with a manual assessment of respiratory rate and breathing pattern at 3 hours. If the neonate meets any criteria of severe instability at any stage of the screening process, they will receive immediate medical management but will be excluded from the study only

if they continue to meet severe criteria at the 3h assessment. All babies will receive standard medical management (E.g. oxygen. IV fluids, IV antibiotics) as indicated by the study site staff and standardised management protocol.
All screening procedures will be documented on the screening log, which will record all new admissions weighing <2000g who undergo screening procedures and the outcome of the assessment. An eligibility checklist and flow chart will be used to assist the screening process. A screening number will be allocated.

It is estimated to take between 30 minutes and 3h 20 minutes to complete the screening process (Appendix 1. Overview of screening and enrolment procedures).

If the baby meets eligibility criteria but the caregiver is not present within 3h of the screening procedures, the 10 minute observation of cardio-respiratory stability will be repeated and documented once the caregiver is available and prior to informed consent. This is to ensure that the baby has not deteriorated in the intervening period.

5.4 Recruitment

5.4.1 Sensitisation

General sensitisation will be conducted at the study site (EFSTH), high risk 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

Informed consent will be sought from the parent/caregivers of all participants for the following neonatal participation: inclusion in the study; collection of socio-demographic data; collection of clinical data; collection of biological samples 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.

The preferred person to provide informed consent for neonatal involvement is the parent. However, it is recognised that this may not be possible within the time-frame due to maternal ill health, admission to another health facility and unavailability of father. An estimated 21% of parents may be unavailable within 24h of neonatal admission (unpublished data). If the parent is not available, it will be explored if there is any alternative caregiver available. This caregiver will most likely be a relative of the mother or father. The caregiver will be given the option of using the study telephone to discuss with the parents. Once the parent is available at the study site, the informed consent process will be repeated with the parent to confirm their consent for their baby to continue participation in the study.

Informed consent for taking maternal/caregiver biological samples will be sought after the neonatal consent procedures have finished and before the intervention begins, using a separate information sheet and consent form.
Impartial and literate witness will be used during consent for illiterate parent/caregivers, as per ICH-GCP guidance.

Further details regarding the informed consent process are detailed in section 11.2.

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 caregiver enrolment number will be allocated and a 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 parent or caregivers details, in the event of the mother not being available immediately and other family members providing the intervention.

5.5 Collection of baseline data

Baseline data will be collected following the informed consent process and before randomisation. The purpose is to record the socio-demographic, clinical, anthropometry and bacterial carriage status of the participants before they receive either intervention or control procedures and for the randomisation and allocation procedures not to be biased by the clinical condition of the neonate.

5.5.1 Socio-demographic data

The following socio-demographic data will be recorded as soon as possible after admission on the eCRF by study personnel:

- Maternal details, including: contact details; tribe; employment; highest level of education; date of last menstrual period; gravidity and parity; significant medical history and ante-natal complications and interventions
- Peri-natal & birth details, including: mode of delivery; presence of septic risk factors; administration of antenatal steroids and antibiotics in preceding 7d; apgar scores
- Neonatal details including: gender; age at admission; multiple birth; interventions since birth (resuscitation; antibiotics; other medications)
- Paternal and household socio-demographic details, to be obtained as soon as is practical

5.5.2 Clinical data

Study personnel will aim to collect clinical data as soon as possible after enrolment, with the exception of gestational age assessment and length measurement, which will take place as soon as possible within 48h of admission. If medical care (E.g. oxygen or IV fluids) has already been started by the study site medical or nursing team this will be continued throughout the assessment and 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.

The assessments will be performed in the following order and all data will be recorded and later entered into the eCRF within a defined time period:

1. The axillary temperature will be measured with a low-reading digital thermometer. Three measurements will be taken and the mean value calculated in degrees Celsius.
2. A blood glucose level will be checked by heel prick using the study specific blood glucose machine and appropriately sized heel prick lancets.
3. Examination
4. Head circumference (occipito-frontal-circumference, OFC) will be measured.
5. Gestational age will be estimated using the New Ballard gestational age assessment score (Appendix 2).
6. Crown-foot length will be measured using a portable measuring mat

The collection of baseline clinical data is estimated to take approximately 30 minutes, not including gestational age and length measurement which may be delayed to within 48h of age (Appendix 1).

5.5.3 Microbiological data

The baseline neonatal rectal and skin swabs will be taken as soon as possible after enrolment, before starting the intervention or control procedures and prior to administration of antibiotics, unless the clinical situation warrants immediate antibiotic therapy.

Paired maternal/caregiver skin and recto-vaginal (RV)(mothers only) swabs will be taken as soon as possible after admission and prior to the neonate commencing the intervention or control procedures. If the mother is not immediately available maternal swabs will be taken before the mother starts any skin-to-skin intervention.

5.6 Randomisation

Randomisation will take place following collection of baseline data and before the intervention or control procedures start. The details of the randomisation method are outlined in section 3.2.1.

5.7 Details of intervention / control

Following completion of the above recruitment procedures and any necessary medical procedures and administration of medications (E.g. insertion of IV cannula, gastric tubes or nasal cannula for oxygen), all neonates will receive the intervention or control care.

5.7.1 Patient flow:

The current admission procedure at the study site is for new admissions to be assessed on a radiant heater in the critical area of the neonatal unit. Depending on the level of stability, the preterm/LBW baby is moved to an incubator or, if severely unstable remains on the radiant heater for close observation. Once off oxygen, IV fluids and clinically stable, neonates are moved to an incubator in the “stable area” or KMC unit, depending on the other clinical problems and availability of KMC unit beds. In the trial, all participants will be managed in the same room of the neonatal unit until clinically stable and then will be moved to the KMC unit, as clinically and logistically indicated and in accordance with standardised management protocol. Discharge from the KMC unit will be according to KMC unit guidelines and follow-up will be as per current KMC unit schedule depending on discharge weight.

5.7.2 Intervention arm

Babies allocated to receive early continuous skin-to-skin contact will be naked except for hat and nappy and will be secured next to the exposed chest of the mother or caregiver using a KMC wrapper. The pulse oximeter will be attached to the subjects hand prior to placing baby in skin-to-skin position. 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 the bed. The oxygen will be provided from an oxygen concentrator and attached to the nasal cannula. If the baby is on IV fluids, they will be connected to the IV cannula and the fluid bag securely hung, with drip rate calculated as per standard practice. Mothers/caregivers will be asked to continue skin-to-skin contact for as long as possible, aiming for minimum 18h/day but recognising that short breaks at regular periods will be necessary. If the mother/caregiver needs to take a short break, the baby will be placed in an incubator or under a radiant heater. Every effort will be made to encourage skin-to-skin contact for minimum 18h/day, unless otherwise clinically indicated and the mother/caregiver will be able to take short breaks as needed. The person providing skin-to-skin contact may change with substitute providers but a primary skin-to-skin, or KMC, provider

will be encouraged to avoid frequent disruption to the baby. The duration of skin-to-skin contact will be monitored. Once the subject is fully stable (definitions, page 10) and a bed is available, they will be transferred to the adjacent KMC Unit.

5.7.3 Control arm

Babies allocated to the control arm will be placed in an incubator or under a radiant heater, as per standard management at the study site. They will wear a hat and be wrapped as per standard care. Oxygen will be provided from an oxygen concentrator and IV fluids securely attached to the IV cannula and 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 stability criteria (definitions, page 10) and is >24h since hospital admission, in keeping with current standard care practices at the study site. The baby will initially receive intermittent KMC (60 minutes after feeds) with the parent/caregiver in a chair next to the incubator or radiant heater in the study area. Once fully stable (definitions, page 10) and not requiring oxygen or IV fluids, the baby will be transferred to the KMC Unit to start continuous KMC.

5.7.4 General procedures for both arms

Although mothers will provide the majority of skin-to-skin contact in both arms, other family members or helpers will be encouraged to assist the mother. The timing, frequency and relation of each substitute caregiver providing skin-to-skin contact will be documented. The dates and times of both starting skin-to-skin contact and changing between types of KMC (intermittent/continuous) will be documented. The duration of skin-to-skin contact will be objectively monitored if possible exact method to be confirmed but options include a tablet based app to record direct time or inbuilt sensors in the KMC wrappers. This data will be used to assess compliance with the intervention and to allow future analysis of the “dose response” of skin-to-skin contact. During time in an incubator or radiant heater, subjects in both arms may co-habit the space, as is currently practised during busy periods on the neonatal unit. Co-habitation will be recorded.

The parent/caregiver in both arms will be educated about the following topics: Infection control and hand washing; breastfeeding and feeding support; danger signs; what to do in the event of an apnoea. These education sessions will take place on a thrice weekly basis for all parents/caregivers at the neonatal unit and will be co-ordinated by the study site team, with support from the research team and in accordance with a pre-defined education schedule.

5.8 Follow-up

Participants will be followed up daily during the hospital admission (see clinical evaluations, section 6.1.2).

If participants are discharged before day 7, they will be phoned on day 7 to ascertain outcome (alive, died, re-admitted) and asked to come to the clinic when 28 days old. If participants are discharged between day 7 and day 28, they will be asked to return to the routine KMC unit clinic on day 28 of life where they will have repeat swab samples (skin, rectal) taken, undergo anthropometry and document feeding practices and outcome (alive; dead). If 28 days falls on a weekend, they will be asked to come on the closest working day (E.g. if a Saturday, come on Friday, if day 28 is Sunday, to come on Monday) with a window period of 5 days (28 days +/- 5 days). 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 as soon as possible. Routine follow-up out with 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 Other study procedures

In-order to conduct a process evaluation of the study and intervention on study outcomes, additional health systems and clinical data will be prospectively collected. This will include:

1. Admission data for all neonatal unit admissions to observe changes in bed capacity; referral patterns; proportion of preterm/LBW admissions and mortality rates, etc
2. Monthly surveys of staffing; equipment; drug availability and infra-structure
3. 6 monthly neonatal quality of care survey, including progress monitoring of KMC provision/services and audit of KMC unit data 6 monthly environmental surveillance of neonatal unit and KMC unit
4. Annual documentation of national health delivery, finances and staffing levels, including national survey of neonatal/KMC provision. This will also include documentation of the costs involved in providing early KMC, to enable a future economic analysis of the intervention.

5.10 Final study visit

The final study visit will be at the hospital KMC unit clinic at 28 days of age, as described in section 5.4.6.

6 STUDY EVALUATIONS

6.1 Clinical evaluations

6.1.1 Evaluations during first 24h of intervention

All subjects will have continuous cardio-respiratory monitoring with a Nonin 2500A pulse oximeter for minimum 24h after intervention/control procedures begin and continued until the subject is stable (definitions, page 10).

Manual auxiliary temperature will be taken 6hrly for the first 24h. The subjects will be reviewed every 6h for manual recording of the respiratory rate and breathing pattern and reviewed at least once by the study clinician during the initial 24h period. An adapted SCRIP score will be calculated post-hoc to quantify cardio-respiratory stability (Appendix 3). Blood sugar measurements will be measured every 6h, unless <2.6 mmol/l in which case it will be measured 1hrly until 2 or more consecutive readings are in normal range (2.6 – 6.9 mmol/l).

6.1.2 Evaluations from 24h to hospital discharge

Starting at 48h of study participation, all subjects will be followed up daily until admission to the KMC unit and then weekly on day 7, 14, 21, 28 of life during the KMC unit stay. If a baby requires re-admission to the neonatal unit the reviews will re-start every day until KMC unit admission or discharge from the neonatal unit. The following actions will be done using study specific equipment:

a. Daily review with the following trial assessments documented:
   - Date and time of starting breast milk feeding and date that full breast milk feeding is established
   - Date and time of starting breastfeeding
   - Daily recording of IV fluid volumes, drip rates and medications given
   - Daily measurement of vital signs (heart rate, respiratory rate, oxygen saturation, temperature, blood glucose)
   - Compliance with the standardised management protocol and discussion of any deviations with study site medical team
   - Documentation of details about skin-to-skin contact:
     - Date and time of skin-to-skin contact initiation
     - Duration of skin-to-skin contact/day
     - Person providing skin-to-skin contact

- Whether skin-to-skin contact is temporarily discontinued and date/time of this event
- Documentation of patient flow through the ward Identification and documentation of any change in clinical condition warranting temporary cessation of intervention and date/time of temporary cessation
- Identification of any SAE

b. Weighed on day 5, then daily until discharge(to be done at an appropriate time in collaboration with study site staff and clustered with other procedures, E.g. changing of nappies)
c. OFC and length to be measured weekly using study equipment
d. Neonatal skin and rectal swab sample to be taken on days 7 and 28 if still an inpatient or attending outpatient clinic

Study site staff will be responsible for the ongoing medical and nursing management of the neonate according to the standardised management protocol with input from the study team if requested.

6.1.3 Evaluations in event of clinical deterioration

Study site staff will be given guidance and training on recognition of signs of severe illness according to adapted PSBI criteria (figure 3) and asked to inform research personnel if a baby fulfils the screening criteria. Research personnel (research nurses or clinician) will then examine the baby as soon as possible, for the presence of any signs of infection (figure 4). The participant will also be assessed for signs of severe illness and infection during the daily in-patient review. If the subject meets criteria for suspected late-onset infection they will have blood +/- CSF cultures taken as soon as possible but not to delay antibiotic administration (section 5.3.2). Once samples have been taken, management will be directed by the study site team in accordance with the standardised management protocol and the research clinician will complete the appropriate safety monitoring documentation. The study personnel will also assess if the baby meets criteria for temporary withdrawal from the intervention arm.

Figure 3. Screening criteria for severe illness

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

(adapted PSBI criteria)
-Refusal to feed / abdominal distension or pre-feed gastric aspirates > 50% of feed volume
-Lethargic (not moving or moving with stimulation only)
-Respiratory rate >80 bpm or severe chest wall indrawing or new oxygen/CPAP requirement
-Apnoea*
-Auxillary temp >37.5
-Auxillary temp <35.5 (after 1h of observed skin-to-skin contact)
-Convulsions

Figure 4. Criteria for investigation of suspected late-onset infection

Take blood +/- CSF culture if clinical deterioration at ≥72h of age and has 1 of:
- Jaundice
- Apnoea*
- Hepatomegaly
- Pallor
- Lethargy or movement only when stimulated

*Spontaneous apnoea with no identifiable reason. (E.g. not associated with milk aspiration, severe respiratory distress or end stage respiratory failure)

6.1.4 Procedures at time of discharge or death

The subject will be discharged according to KMC unit discharge criteria by study staff.
The following will be documented on the eCRF within 24h of discharge or death:

- Date and time of discharge or death; Cause of death; Most recent weight before death/discharge; Details of feeding at time of death/discharge.

At time of discharge, the parent/caregiver will be given pictorial information about danger signs and instructed to contact the study team or seek medical help if the baby becomes unwell before 28d of age. They will be provided with the study team contact numbers and a study participant ID card.

6.1.5 Procedures at follow-up

At the day 28 follow up they will be seen by study personnel, have repeat swab samples taken, undergo anthropometry (measurement of weight, OFC and length) and be asked about general health and feeding practices.

6.2 Microbiological evaluations

The following is a summary table of all biological samples to be taken during the study:

Table 1. Summary of all biological samples to be taken during clinical study

Source	Type of sample	Site of sampling	Timing	Purpose
Neonate	Swab samples	Rectal Skin	D0, 7, 28	Storage for future ESBL-gram-negative bacilli carriage & molecular analysis
	Blood culture	Peripheral venous blood	If suspected LOS	To confirm LOS & storage for future molecular analysis
	CSF culture	Lumbar puncture	If suspected LOS	To confirm LOS & storage for future molecular analysis
Caregiver (if mother not immediately available)	Swab sample	Skin	Before starting KMC	Storage for future molecular analysis
Mother	Swab sample	Recto-vaginal Skin	Before starting KMC	Storage for future ESBL-gram-negative bacilli carriage & molecular analysis
Environment	Swab samples	Surface swab samples Aliquots of IV fluid and IV antibiotic	6 monthly intervals before and during study period	Identification of outbreaks, gram-negative reservoirs & storage for future molecular analysis

6.2.1 Collection of swab samples for storage
Size specific FLOQ swab® will be used and all swabs inserted into Amies transport medium at time of collection.

Neonatal skin swabs will be taken as a composite swab from the xiphisternum and the peri-umbilical area. Rectal swabs will be taken by inserting the swab into the rectum and rotating gently.
Maternal RV swabs will be taken by inserting the swab first into the vagina, then into the rectum and rotating gently. Maternal skin swabs will be taken from the xiphisternum. All procedures will be detailed in the Biological Samples SSP.

6.2.2 Investigation of suspected neonatal late-onset infection
Detection of LOS in preterm infants is challenging, especially in the absence of laboratory measurement of inflammatory (FBC, CRP) or severe illness (pH, Base excess) markers. The clinical definition of sepsis used here is based on an internally validated score from very preterm (<33 weeks) hospitalised neonates with blood or CSF culture positive sepsis at >72h of age in a similar resource limited setting.[2] The score has sensitivity of 77.1%, PPV 64.9% (AUC0.70, n=497) compared to blood culture and is the considered the most suitable clinical score for the population and local context.

6.2.2.a. Blood cultures
In the event of a clinical deterioration during hospital admission which meets criteria for possible late onset infection (figure 4), blood cultures will be taken as soon as possible and before antibiotics are started or changed, if possible. If there is a delay in obtaining the biological samples, this will not delay the administration of antibiotics by study site staff. Blood cultures will be taken according to a study specific Biological Samples SSP.

6.2.2.b. CSF cultures
A lumbar puncture will be performed as soon as possible during normal working hours if late onset infection is suspected according to pre-defined clinical criteria and if there are no clinical contra-indications (raised intracranial pressure; active bleeding; severe cardio-respiratory instability (definitions, page 10); soft tissue infection or congenital malformation at the puncture site). It will be performed in accordance with a study specific Biological Samples SSP.
Both procedures will be carried out with appropriately sized needles and skin antisepsis with precautions to avoid contamination.

6.2.3 Environmental surveillance
Infection control procedures will be regularly documented and environmental surveillance of the neonatal unit and KMC unit will take place at 6 monthly periods at the start of and throughout the study period to identify any external changes in infection control practices affecting outcomes and for future analysis of transmission dynamics. The swab sites will be based on locally available infection control data, possibly include key surface swabs, culture of IV fluids and IV antibiotic vials.

6.2.4 Sample labelling, handling & transport
All biological samples will be collected and handled in a standardised manner according to study specific protocols. Pre-printed labels will be used for each sample and hand labelled with the date and time only. Sample transport logs will be used to document and track the movement of samples between the study site and MRCG Clinical Laboratory.

Swab samples
Swab samples will be kept in a temperature monitored fridge at the study site at between +4 and +8^{o}C whilst awaiting transport. Samples will be transported in a temperature monitored transport cool box with ice-packs to the MRC Clinical Laboratory within 6 hours of collection. If samples are taken during out-of-hours periods, they will be stored at the SMAC laboratory at the study site in a temperature monitored fridge at 4 to 8 ^{o}C for maximum 48h. The temperature of the transport cool box will be documented at time of leaving the study site and arrival at the MRCG Clinical Laboratory.

Blood culture samples
Inoculated *BACTEC Peds* Plus™/F culture vials will be transferred to the MRCG Clinical Laboratory as soon as possible. If this is likely to be delayed, the sample will be kept at room temperature and transferred to the lab within 24h

Cerebro-spinal fluid (CSF) samples
The CSF samples will be transported to the MRCG Clinical Laboratory within 1h of collection, during normal working hours.

7 LABORATORY EVALUATIONS

7.1 Storage of carriage samples for future processing

Neonatal and maternal/caregiver rectal/recto-vaginal will be vortexed for 30 seconds then divided into two 500 microlitre aliquots with 1 sample including 50 microlitres of glycerol 50% for future microbiological culture. Skin swabs will be stored in original cryovial with no processing.

7.2 Evaluation for aetiology of late-onset infection

7.2.1 Blood culture & antibiotic sensitivity testing
Blood cultures will beentered into the automated Bactec® 9050 BD machine at MRC Clinical laboratory. All samples showing a positive signal will undergo sub-culture using standard methods and in accordance with MRC Clinical Laboratory SOPs. Antibiotic sensitivity testing will be performed according to CLSI 2017 guidelines. Positive isolation of a recognised neonatal pathogen will be considered to be significant.

7.2.2 Cerebro-spinal fluid (CSF) microscopy & culture
The CSF sample labelled for microbiological analysis will undergo macroscopy, microscopy, culture and antibiotic sensitivity testing of any isolates, as per MRCG SOP ASSAY-CLA-210. Microscopy will give the cell count and gram stain. Culture will be done with Chocolate, Blood and MacConkey agar media with identification of any isolates according to MRCG SOP ASSAY-CLA-210 and antibiotic sensitivity testing as per MRCG SOP ASSAY-CLA-212.

The CSF sample labelled for biochemistry will be analysed for glucose and protein levels, as standard practice. Any leftover specimen will be stored at -70 ^{o}C for future testing to identify bacterial pathogens using molecular techniques (PCR).

Isolation of organisms such as Coagulase Negative Staphylococcus (CONS), Diptherioids, *Bacillus* spp. and mixed growth from blood or CSF culture, will be considered as contaminants but will be identified and documented by laboratory staff.

7.3 General considerations

All laboratory procedures will be carried out according to study specific protocols and in accordance with relevant MRCG Clinical laboratory SOPs. All isolates and samples will be stored at -70 degrees Celsius at the Clinical Laboratory and transferred to biobank in batches for storage at -80 degrees Celsius for future characterisation.

8 SAFETY CONSIDERATIONS

8.1 Monitoring of study participants

All study participants will undergo continuous cardio-respiratory monitoring for minimum 24h after enrolment and until stability criteria are reached using the Nonin 2500A handheld pulse oximeter, which will measure and record oxygen saturation and heart rate. Alarms will be set to detect bradycardia (heart rate <100 bpm), tachycardia (heart rate >200bpm) and hypoxia (SPO_2 <88%). If at any stage subjects receiving the intervention have features of severe instability (definitions, page 10) which do not improve with tactile stimulation over 5 minutes, they will be removed from skin-to-skin contact and taken to a radiant warmer for further assessment by the study site health workers.. If the subject responds quickly and vital signs normalise and remain within normal range for 15 minutes, the subject can be returned to skin-to-skin position. If the vital signs do not normalise or the subject requires bag-valve-mask ventilation, the baby will remain on the radiant warmer and receive any appropriate interventions and be temporarily withdrawn from intervention arm (section 11.2). The pulse oximeter will remain attached to the subject until he/she meets criteria for being stable (definitions, page 10) and for 24h after an apnoeic event. If a previously stable baby has a clinical deterioration requiring bag-valve-mask ventilation, or meets criteria for severe instability they will re-commence continuous cardio-respiratory monitoring until 24h after the last episode of bag-valve mask ventilation. If a subject is classed as being severely unstable, a research nurse or study site nurse will contact the research clinician or PI (by telephone if at weekend or night) as soon as possible to inform them of the condition for the participant to be screened for possible infection. The management of the baby will be according to the standardised management protocol, as directed by the study site staff.

8.2 Adverse events

See definitions, page 10, for general definition of AE. For the purposes of this study, it will include but is not restricted to the following:

- Deterioration in clinical stability, as per study definitions of stability
- Clinical deterioration as per adapted PSBI criteria
- Any other deterioration needing change in management, out-with routine management
- Abnormal investigation
- Detection of congenital malformation not apparent at time of recruitment

AE will be pre-defined and all AE will be recorded in the SMR, Adverse Event Log and eCRF and reported as below.

8.3 Serious adverse events (SAEs)

The definition of SAE for this study is:

- Death
- Life threatening event
    - Apnoea needing bag-valve-mask ventilation but not resulting in death
    - Severe instability (as per protocol definition)
    - Any other life threatening situation as assessed by clinician
- At risk of permanent / temporary disability
    - Clinically suspected or microbiologically confirmed meningitis
    - Severe jaundice needing phototherapy/exchange transfusion

- Suspected Hypoxic Ischaemic Encephalopathy (moderate-severe)
- Acquired hydrocephalus needing diuretics or surgical intervention

- Re-admission to hospital following discharge and within 28d of age
- Prolonged hospitalisation for 28 days or greater

8.4 Responsibilities for safety

London School of Hygiene & Tropical Medicine is the sponsor for this study. Delegated responsibilities will be assigned locally.

The sponsor (LSHTM) is responsible for the following safety aspects:

- Ensuring that before the study begins there are arrangements in place to allocate responsibilities for the management, monitoring and reporting of the research to be conduct
- Ensuring there are appropriate arrangements in place to record, report and review any significant developments throughout the lifespan of the study
- Management of the adverse event reporting in collaboration with the PI and research team

The principal investigator (PI) will assume responsibility for:

- Reporting all SAEs within agreed timeline to Sponsor and relevant ethics committees
- Provide the sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety within the agreed timeframes specified in the protocol
- Assess each event for causality and seriousness between the research procedures and the adverse event
- Supply the sponsor, relevant ethics committees and other relevant organisations with any supplementary information as requested

The research clinician is responsible for identifying AE, SAEs to the PI within the agreed timeframe and for preparing the SAE reports for submission to the Sponsor. The local safety monitor is responsible for reviewing all SAEs and AEs within the defined time period.
The above responsibilities are based on the LSHTM-SOP-009-01 (SOP. Recording, Managing and reporting Adverse Events for Clinical Trials of Non-Investigational Medicinal Products (Non-CTIMPS).

8.5 Reporting procedures

To monitor for the incidence of adverse events (AE) during the period of hospitalisation, study personnel will review participants daily.

Any adverse events will be recorded in the standardised medical record and eCRF, including any treatments used by study site staff. Study site staff will be responsible for treating any AE with input from the research clinician and PI, as requested. The research clinician will review all AE and classify serious adverse events according to the protocol. All SAE will be reviewed by the PI or delegate within 24h of notification.
The PI or delegate will send an initial notification to the local safety monitor (LSM), sponsor and Clinical Trials Support Office at MRCG within 24h of first being aware. The initial detailed SAE report will be sent to LSM, sponsor and CTSO within 2 working days if the baby dies, or within 5 working days if the baby does not die. The DSMB will receive a 2 monthly summary safety report of all SAE's, as per DSMB charter. Any SAE thought to be related to the intervention will be reported to the ethics committees within 7 days if it results in death or 14 days if non-fatal. All SAE's resulting in death but not related to

the intervention will be submitted to ethics committees as a monthly summary. All other (non-fatal) SAE's will be reported as an annual safety report to ethics committees and the sponsor.

Reporting procedures will be outlined in an Adverse Event SSP. All SAE reports or other safety reports will be kept as essential documents in the Trial Master File.

8.6 Safety oversight

A local safety monitor and an independent Data Safety Monitoring Board (DSMB) will review all the SAE during the course of the trial, as detailed in section 8.1 & 8.2 and outlined in the DSMB charter.
The local safety monitor will be a consultant paediatrician with experience of neonatal care at the study site and an understanding of the limitations of the current standard care. An independent DSMB will be established consisting of an experienced statistician (chair), a paediatrician or neonatologist and a clinical trialist, all with experience in Sub Saharan Africa. The DSMB will meet in person or remotely before the trial begins, every 6 months during the study, following interim and final analysis and at any other time as requested by DSMB. The DSMB will examine SAEs, rate of enrolment, follow-up and compliance to the intervention. An interim analysis will be suggested to the DSMB, to be conducted when approximately half the intended subjects have been followed-up. As this is an un-blinded study, there will be no code to break. The DSMB will advise the study team on study modification, continuation or termination based on pre-defined stopping rules. The sponsor will receive a yearly update report about the study, including summary of safety issues.

9 DISCONTINUATION CRITERIA

9.1 Participant's premature termination of intervention

9.1.1 Criteria for temporary with-drawal from intervention arm
Participants will stop the intervention if any of the following criteria apply:

"Stopping criteria":

1. Severely unstable for >10 minutes if:
   - ✓ SPO2<88% in oxygen

   AND ≥1 of:
   - ✓ Respiratory rate <20 or > 100 breaths/min
   - ✓ Severe chest in-drawing
   - ✓ Apnoea needing bag-valve-mask ventilation
   - ✓ HR <100 or >200 beats/min

   OR CPAP is required on clinical grounds as per Standardised Preterm Management Criteria

2. Any other condition which precludes continuous skin-to-skin contact
   a. Severe jaundice needing immediate management
   b. Severe anaemia needing blood transfusion
   c. Seizures
   d. Severe abdominal distension
   e. Omphalitis or infection of the umbilical cord
   f. Apnoea needing 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

9.1.2 Criteria for re-starting skin-to-skin contact after temporary withdrawal

It is standard practice at the study site to commence intermittent skin-to-skin contact (KMC) once the baby is stabilising and off oxygen but may still be receiving IV fluids or IV antibiotics. If a baby leaves the intervention arm due to clinical instability but then later improves, they can re-start intermittent skin-to-skin contact once all of the following criteria are met, in-line with the current standard care provided at the study site:

"Re-start" criteria:

- No apnoea requiring bag valve mask ventilation for 24h
- Stable (see definitions, page 10)
- No severe chest in-drawing
- No seizures for 24h
- No abdominal distension
- Not on oxygen
- Not on phototherapy for severe jaundice
- Mother or caregiver available and willing to do skin-to-skin contact
- No health care worker concerns about the clinical condition

If the baby requires IV medications or IV fluids but otherwise meets the re-start criteria, intermittent skin-to-skin contact (KMC) can still be recommenced. The baby can be transferred to the KMC unit for continuous skin-to-skin contact once the "re-start" criteria are met (above) and the subject is not receiving IV fluids.

The above criteria for starting intermittent and continuous skin-to-skin contact will apply to the control arm as well as the intervention arm.

9.2 Study discontinuation

Stopping rules will be set by the DSMB prior to the study starting.

10 STATISTICAL CONSIDERATIONS

10.1 Sample size

A total of 392 subjects are required to show a 30% relative reduction in the primary outcome of all-cause mortality at 28d (power 80%, alpha=0.05). This is based on feasibility study data indicating a mortality rate in eligible neonates of 56% at 28d of age (adjusted to 48% for an estimated 15% reduction in mortality due to trial processes). The number of subjects lost to follow up is expected to be negligible (<5%), due to the geographical region involved, follow-up system planned and based on feasibility study results. However, the number of subjects lost to follow-up will be reviewed at 3 months of recruitment and any necessary adjustments to the sample size will be made, in collaboration with the DSMB.

With the estimated sample size of 392, all secondary outcomes have a power of at least 70%.

10.2 Recruitment plan & timelines

Based on published admission audit data from the study site[10] and observed prevalence of eligibility criteria in the target population (unpublished data), between 135 - 245 clinically eligible subjects are admitted to the study site annually. It is

expected that mothers and fathers may not be present within 24h of admission in 20% of cases and enhanced sensitization and consenting procedures will be used to overcome this recruitment barrier.

Recruitment will take place over 24 months according to a pre-defined recruitment plan with adjustments for seasonality of preterm/LBW births and local admission rates. The weekly recruitment target will vary from 4 to 6 (average 17 subjects/month). The TSC and DSMB will review the recruitment rate at regular periods and any necessary adjustments to the recruitment plan will be made.

10.3 Statistical analysis

A statistical analysis plan will be completed prior to recruitment. Data will be analysed using Stata version 15. P values <0.05 are considered significant.

Comparison of participants in two arms
Analysis will be performed with number of subjects in each arm as the denominator. Summary values (means, proportions) for the following variables will be compared between arms for any imbalances: socio-demographic data (mean age at enrolment; mean gestational age; mean weight; maternal ante-natal, peri-natal and social details); baseline clinical status (stability, mean temperature, mean blood glucose). Compliance to key indicators from Standardised Management Protocol will be compared in both arms.

Flow of participants
The number and flow of subjects through eligibility screening, randomisation, allocation, temporary withdrawal and follow-up will be documented, as per CONSORT 2010 guidelines.[24] Reasons for exclusions and withdrawals will be described.

Primary & secondary outcome analysis
The number of subjects who meet criteria for the primary outcome will be calculated for each arm and chi-squared test will be used to test for intervention efficacy. This will be presented as an appropriate effect size with a measure of precision (E.g. 95% confidence interval).
Analysis of secondary outcomes will be performed according to type of data and using either number of subjects or person time as the denominator, as appropriate. A survival analysis will be performed for the time to event outcomes (time to death, etc).
Appropriate adjustments will be made to account for clustering of death within multiple birth subjects and for other confounding factors.

Subgroup analysis
Subgroup (secondary) analysis for all outcomes will be performed for infants according to birth weight categories, and duration or “dose” of skin-to-skin contact. The relative measures of effect within each of these subgroups will be estimated.

Analysis of arms according to intervention adherence
Analysis of primary and secondary outcomes will be conducted on an intention-to-treat basis.

Additional analysis
Logistical regression will be used to explore risk factors for the following outcomes: mortality at 28d; near death within 24h; and confirmed late-onset infection (including validation of existing nosocomial sepsis predictive scores). At the end of the

study a pre-post comparison of in-patient mortality incidence with be conducted as part of the process evaluation. This will use published mortality data from the pre-study period [10] and prospectively collected mortality data during the study period.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data management and processing

11.1.1 Types of data

Quantitative data on socio-demography, anthropometry, clinical examination, gestational age, cardio-respiratory stability status, temperature and blood sugar measurements, clinical progression, hospital treatments, outcomes and microbiological samples will be collected. Data will be dichotomous (e.g. alive/dead) or numeric (e.g. weight in g). Laboratory data will be dichotomous (e.g. culture positive for specific bacteria).

11.1.2 Format of data

Quantitative data will be collected on paper forms (screening log, patient flow log, cardio-respiratory stability measurement log, gestational age assessment sheet etc) or entered directly onto an electronic clinical record form using RedCap® software on a study tablet at the study site. The electronic case record form (eCRF) will be developed by the PI and data manager. A data dictionary will be generated using a standard template. Standard data coding will be used with in-built quality control checks. Electronic cardio-respiratory and temperature measurements will be downloaded onto an Excel spreadsheet and reconciled with the main electronic database. Once available and authorised, paper laboratory forms will be reconciled with the main electronic database.

11.1.3 Methodologies for data collection / generation

The handheld maternity record card, partograph, referral letter and investigation results will act as source data at time of enrolment, in addition to direct verbal questioning of parent/caregiver. Vital signs, clinical examination, anthropometric measurements, daily progress and treatment/feeding details will be recorded daily during the daily study review and documented on the hospital medical record with additional paper forms to help structure the data collection. Continuous heart rate and oxygen saturation levels will be recorded and stored on the Nonin 2500A pulse oximeter and transferred to a secure, password protected computer via connector cable after monitoring ends. The data will be analysed with the nVISION® software and the results of analysis will be entered into the eCRF.. A Data Transfer SSP will outline the methods of identifying electronic data measurements and ensuring correct participant allocation.
Data on neonatal mortality and date of discharge will be recorded from ward admission/discharge books and death certificate books. Cause of death will be determined following research clinician review of the medical record and in consultation with a Consultant Paediatric (PI). All study personnel will undergo training in data collection and storage.

11.1.4 Data Storage & security

Photocopies of source documents will be stored in participant study folders at the study site. The raw data from the pulse oximeters will be downloaded to the central server as soon as possible after completion of recording and the file name will be recorded on a transcription log, in accordance with Data Transfer SSP. No data will be stored on the study site computer. All computers used for data storage will be password protected with access restricted to essential study personnel and co-PIs only..

The eCRF records will be transferred to the secure network server at MRCG at regular, predefined intervals. The electronic study database will be password protected and accessible in line with the MRC Corporate Information Security Policy and the MRC's Information and Communication Technology Security Policy. Users will be granted access based on their

research roles.
There will be restricted access to the secure network server and this will be backed up as part of MRC's disaster recovery plan. Daily and monthly backups of all media servers occur and a dedicated project folder for archiving of electronic files will be created

The long-term storage of research records will be done in accordance with the LSHTM and MRC's policies and procedures for archiving.
The electronic study database will be password protected and accessible in line with the MRC Corporate Information Security Policy and the MRC's Information and Communication Technology Security Policy. Users will be granted access based on their research roles.
The main data security risk is a compromise to the confidentiality of study subjects. No subject identifiable information will be entered into the electronic database. All such data will be stored in a filing cabinet in the locked study office, to which only the study personnel and PI will have access.

All paper data collection forms, eCRF, raw cardio-respiratory stability and photographs of source documents will be held securely by the Unit and shared according to the LSHTM and MRC's policy on research data sharing and preservation. Anonymised data generated within the study will be suitable for sharing in CDISC ODM (international standard) format with other interested researchers.
The Principal Investigators will maintain appropriate medical and research records for this study in compliance with the principles of GCP and regulatory and institutional requirements for the protection of confidentiality of participants.
The authorised representatives of the sponsor, the ethics committee(s) or regulatory bodies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

11.2 Source documents and access to source data

11.2.1 Source documents

The maternal hand-held antenatal card, referral letters, partographs and investigation reports will be source documents for maternal and perinatal socio-demographic details. The neonatal unit death certification book and ward report book will be used to document the date and time of death.
The hospital medical record and nursing ward round book will be used throughout the hospital admission as a source document with additional structured CRF's to document the study procedures, daily reviews and clinical deterioration.

A separate screening document will be used to document the cardio-respiratory and examination findings during the screening process and baseline data collection. A patient flow schematic will be used to document the movement of the subjects around the neonatal unit.

11.2.2 Access to source data

All source documents will be held securely by the Unit and shared according to the LSHTM and MRC's policy on research data sharing and preservation. Anonymised data generated within the study will be suitable for sharing in CDISC ODM (international standard) format with other interested researchers.

The PI will maintain appropriate medical and research records for this study in compliance with the principles of GCP and regulatory and institutional requirements for the protection of confidentiality of participants.

The authorised representatives of the sponsor, the ethics committee(s) or regulatory bodies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

12 PROTOCOL DEVIATIONS

A protocol deviation (PD) is any noncompliance with the clinical trial protocol, good clinical practice (GCP), or other applicable regulatory requirements. The noncompliance may be either on the part of the participant or the investigator including the study team members, and may result in significant added risk to the study participant. Deviations will be pre-defined as either major or minor. In the event of a major deviation, corrective actions will be deployed and implemented promptly. A deviation log will be kept.

If a deviation from, or a change of, the protocol is implemented to eliminate an immediate hazard(s) to trial participant without prior ethics approval, the PI or designee will submit the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) as soon as possible to the sponsor for agreement and the relevant independent ethics committee (IEC) for review and approval.

The PI or designee will document and explain any deviation from the approved protocol on the eCRF, where appropriate, and record and explain any deviation in a protocol deviation form that will be maintained as an essential document.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Socio-demographic data entry

The Redcap software will include in-built quality control checks, including range checks, precision to pre-defined decimal point and mandatory fields. The eCRF for a particular subject will only be closed once all essential data has been collected, to reduce rates of missing data. Quality control checks will be performed through-out the study by cross checking the source document and the entered data at random times within a defined period. Any missing socio-demographic data will be obtained as soon as possible.

13.2 Clinical data measurements

The quality of data collected will be ensured by performing inter-observer standardisation checks for head circumference, length and assessment of gestational age. This will be done during study personnel training and also randomly checked at pre-defined intervals during the data collection process. The digital weighing scale will be calibrated daily and the fluid level checked prior to use with adjustments made as necessary to ensure an accurate weight is obtained. The scale will be plugged in to re-charge the battery at predefined intervals and according to the manufacturers guidelines. Pulse oximeters will have re-chargeable batteries replaced at the end of each subjects monitoring period and research personnel will be trained on how to recognise and document a high quality reading on the pulse oximeter.

13.3 Laboratory processes

All biological samples will be processed at MRC laboratories in accordance with internal quality control procedures (MRCG SOP-CLA-010). All positive results will be reviewed and authorised by a Consultant Microbiologist.

13.4 Staff training

MRC research personnel will undergo detailed training on study objectives, study schedule, all study procedures and SSPs. This will include detailed informed consent training in the local languages, as per the Joint Gambia Government/MRC Ethics Committee approved training. Nurses at the study site will undergo training about the study objectives, study schedule and procedures. Training for all staff (MRC and study site) will include the following topics to ensure nursing and medical care

is appropriate: recognition and management of a sick baby; resuscitation skills; standardised preterm/LBW management protocol.

13.5 Study monitoring

The monitoring plan will be approved by the sponsor before recruitment starts. A trial monitor from MRCG will monitor the informed consent process, study documentation, including Study Master File, Delegation log and other essential paperwork as per ICH-GCP guidance. A site initiation visit will take place prior to recruitment starting followed by 3 monthly interim visits by trial monitor and a closing visit at end of the study. All monitoring forms, reports and correspondence will be filed in the Study Master File.

The study may be subject to 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.

14 ETHICAL CONSIDERATIONS

14.1 General considerations on human subject protection

This study is conducted in accordance with the principles set forth in the ICH Harmonised Tripartite Guideline for Good Clinical Practice and the Declaration of Helsinki (Appendix 4) in its current version, whichever affords the greater protection to the participants.
Local ethical approval will be provided by the Gambia Government / MRC Joint Ethics Committee in addition to ethical approval from London School of Hygiene and Tropical Medicine (LSHTM) Ethics Committee, prior to recruitment starting.

14.2 Rationale for participant selection

The focus of the clinical trial is initiation of continuous skin-to-skin contact within 24h after birth in all hospitalised preterm/LBW neonates with the exception of:

- Those unlikely to survive the first 24h after birth, regardless of study arm (E.g. severely unstable at time of admission and assessment; major congenital malformation)
- Neonates in which continuous skin-to-skin contact is impractical due to clinical and logistical reasons (E.g. no caregiver available or willing to do continuous skin-to-skin contact; seizures)
- Those who are stable and should receive KMC, as per WHO recommendations

14.3 Evaluation of risks and benefits

14.3.1 Risks

This non-pharmacological clinical study is considered to be low risk to subjects compared to current standard care at the study site. Risks to participants include the following:

14.3.1.a Potential risks from the intervention (early continuous skin-to-skin contact, as part of KMC)

Skin-to-skin contact, or KMC, is recognised as being a very safe intervention for stable preterm/LBW babies and perceived risks about obstructive airway due to head positioning and during mother's sleep are not proven in either the available literature[11] or anecdotal experience of international KMC experts (personal communication, Dr Van Rooyen). Recent

evidence from a neonatal intensive care setting in a HIC demonstrated no difference in cerebral oxygenation in preterm infants receiving skin-to-skin contact and respiratory support (endotracheal intubation and mechanical ventilation; nasal CPAP or high flow nasal cannula) compared to incubator care.[22] However, the safety profile of using early continuous skin-to-skin contact in unstable babies in a resource limited setting without adequate clinical monitoring is less well established[14] and there is the theoretical possibility of adverse events such as: airway obstruction due to poor positioning; dislodgement of oxygen nasal prongs causing worsening of respiratory distress and late or missed recognition of a critically ill baby needing resuscitation.

As there are currently no local neonatal intensive care facilities, no options for continuous cardio-respiratory monitoring and the current case fatality rate is high, the risks of the intervention are not likely to be higher than standard care, but every effort will be made to identify and minimise them.

Steps to reduce risk in intervention arm:
Ensure that all study personnel and study site staff undergo training in KMC, including proper positioning of the baby in skin-to-skin position; recognition of danger signs and neonatal resuscitation

- A pilot phase of providing the intervention in unstable babies will take place at the start of the recruitment phase. This will replicate the study procedures and include a trial of data collection tools. There will be close supervision from the PI during this pilot and any issues with providing the intervention alongside other treatments, study procedures or issues with monitoring, will be addressed prior to the clinical study starting.
- High quality pulse oximeters will be used in all subjects to provide continuous cardio-respiratory monitoring until stability criteria are met. As well as for measurement of outcomes, this is to ensure episodes of apnoea, oxygen saturation and bradycardia are detected in a timely manner. The alarm limits on the pulse oximeters will be set at levels that will alert both caregivers, study personnel and study site staff to any possibility of severe instability (see definitions, page 10).

14.3.1.b Potential risks from study procedures

Risks from anthropometry:
Preterm/LBW babies often don't tolerate multiple procedures and handling. Performing additional anthropometry procedures such as weight and length measurements is potentially de-stabilising for these participants and may result in episodes of apnoea or oxygen desaturation. Currently at the study site babies are weighed on scales with a 10g gradation which is not accurate enough to be used for the study weight measurements. It is recognised that duplication of the weighing procedure may pose an additional risk to the baby so the study weighing scales will be made available to the study site staff to use for measurement of all new admissions. The length measurement will be delayed to within 48h after admission to avoid exposing babies to multiple procedures within a short time frame.

Risks from blood sugar sampling:
Obtaining the blood glucose level by heel-prick sampling can sometimes cause distress, pain or osteonecrosis to the baby, but all measures will be taken to minimise this risk. Size appropriate lancets will be used and the procedure will be carried out according to a study specific protocol with training on the correct site and method of obtaining the sample
.Risks from neonatal/maternal swab samples:
Obtaining neonatal and maternal swab samples is a minimally invasive procedure and will be performed in a careful and aseptic manner according to study specific operating protocols with due attention paid to safe handling and disposal of biological waste. There are no anticipated side effects to the participant. It is acknowledged that some mothers may prefer not to undergo a recto-vaginal swab in the immediate post-natal period but 96% (24/25) of women approached for recto-

vaginal swabs in the feasibility study consented to this procedure. Every effort will be made to obtain the maternal recto-vaginal swabs in a sensitive and un-distressing manner and the procedure will be carried out on an examination bed in a private room. The mother will have the option of refusing consent to the recto-vaginal swab.

Risks from neonatal blood culture sampling:
Obtaining blood for blood cultures is an invasive procedure and all research personnel will be trained according to study specific protocols. The minimum volume of blood required for culture is 1ml and the sensitivity of the investigation increases as the more blood is analysed. However, there are risks to the baby from taking too much blood, including: iatrogenic anaemia with worsening of hypoxia and increased need for blood transfusion if repeated blood samples are taken. This risk is particularly relevant for LBW babies, who have a lower circulating blood volume. To minimise this risk, only 1ml of blood will be taken for culture.

Risks from neonatal lumbar puncture:
In general a lumbar puncture is a safe and well tolerated procedure but there are specific contra-indications for obtaining CSF samples in neonates, including raised intracranial pressure, active bleeding and severe cardio-respiratory instability. This is to avoid the risk of coning, bleeding and sub arachnoid haemorrhage and precipitating apnoea or worsening respiratory distress from holding the baby in the recommended position. A lumbar puncture will not be performed if any contra-indications are present. Research personnel will be trained in performing lumbar punctures according to the Biological Samples SSP. Only the research clinician will be permitted to perform the procedure and the research clinician will discuss the case with the PI before starting the procedure.

Risks of subject movement around the neonatal unit:
The transfer of babies between areas within the neonatal unit is a potential risk for baby becoming hypothermic or unstable. However, as the distances involved are very small, it currently takes place as part of standard care and the baby will be receiving continuous cardio-respiratory monitoring during the transfer, enabling any deterioration to be identified quickly and appropriate measures provided (E.g. resuscitation).

14.3.2 Benefits

14.3.2.a Benefits for Individuals Enhanced clinical monitoring
Currently, critical patients at the neonatal unit have cardio-respiratory monitoring performed once a day as part of the ward round with additional heart rate, respiratory rate and oxygen saturation checks as directed by the doctor and if the patient is severely unstable. As part of this study, subjects will have continuous heart rate and oxygen saturation monitoring until the subject reaches full stability criteria (definitions, page 10). The benefits of continuous monitoring include audible alarms to alert health care staff that resuscitation may be needed and early identification of sick newborns needing other interventions or a change in management.

Availability of microbiological investigations
At present, blood cultures are not routinely available to patients at the study site. The availability of blood culture results will benefit babies who clinically deteriorate and develop infection, by providing information on the invasive bacteria and antibiotic sensitivities. In the event of a positive blood culture, the laboratory staff at MRCG will inform study personnel as soon as possible, who will discuss the results with the study site doctors and change the antibiotic treatment according to the preterm/LBW standardised management protocol.

Access to clinical care at MRCG
The mother and baby will be entitled to receive care at the MRC Gambia Clinical Services Department for the first 28d of the baby's life. As there is no neonatal unit at this hospital the neonate will not be transferred to receive care here, but following discharge the mother may wish to access the health service if she or her baby develops complications. This is standard MRC Gambia practice for study participants. In addition, if a study participant requires any tests that are not available at the study site, they will be able to access them through the MRCG Clinical Services and facilitated by the study team.

14.3.2.b Benefits for health-care system
In the long-term the introduction of continuous KMC will benefit the study site hospital (EFSTH) by reducing the work load for neonatal staff; promoting early discharge and reducing the burden of neonatal unit over-crowding; continuing professional development of neonatal unit staff with KMC training and development of protocols to guide the management of preterm/LBW neonates.

The storage and future analysis of environmental and invasive isolates will provide important information about the epidemiology of hospital acquired infections in this population and may provide a platform for future research in this area. The antibiotic sensitivity profile of gram-negative bacilli will contribute towards the understanding of local antibiotic resistance patterns and the development of local and national anti-microbial prescribing policies.

14.4 Sensitisation

It is not feasible to conduct individual sensitisation or antenatal consent for this study as it is not possible in the local context to identify which pregnant women will give birth to a preterm/LBW baby. However, group sensitisation of expectant mothers and families at "high-risk" antenatal clinics at the major referral sites will take place prior to and through-out the study to educate potential families about the study, the recommendation for KMC in stable babies and the KMC unit. Following admission of the baby to the neonatal unit, parent or caregiver will be sensitised about the study and verbally invited to participate. If they agree, they will undergo the consent process. Details of any sensitisation will be recorded on the eCRF

14.5 Informed consent

14.5.1 Background to informed consent process
There are recognised challenges in obtaining parental consent in neonatal research involving sick newborns with a time limited intervention[23] in resource limited settings. Alternative approaches include parental assent with later full consent or, if locally acceptable, consent from an alternative relative who is present with the baby and has permission to provide consent on the parents behalf.

14.5.2 Informed consent for neonatal participation

Timing of consent
Written, informed consent will take place as soon as possible following screening procedures and prior to randomisation.

Content of informed consent
Informed consent will be taken for the following: neonatal inclusion in the study; randomisation and receipt of the intervention; provision of continuous skin-to-skin contact if allocated to the intervention arm; collection of socio-demographic data; collection of clinical data; collection of biological samples and follow-up.

Person providing informed consent on behalf of the subject

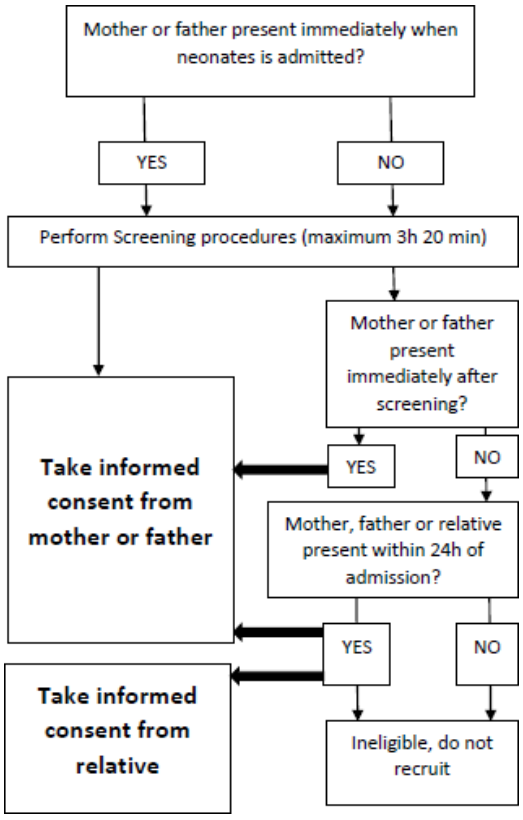
The preferred person to provide informed consent is the parent, but it is recognised that this may not be possible within the time-frame, as outlined in section 14.5.1. If the parent is not available within defined time points (figure 3), it will be explored if there is any relative available. The relative, or caregiver, will then consent on the parents behalf, obtaining verbal permission from the parents via telephone contact if the caregiver wishes. A Statement of Guardianship form will be completed to document the details and relationship of the guardian to the baby. Once the parent is available at the study site, parental informed consent will be obtained to ensure that they agree for the baby to continue in the study.

14.5.3 Informed consent for maternal swabs/caregiver swabs

Written informed consent for obtaining maternal/caregiver swabs will be taken after consent for the neonates participation but prior to any maternal/caregiver samples being obtained. All participants will have the option of declining to have a particular swab taken (E.g. recto-vaginal) if they are not comfortable with the procedure.

Within the intervention arm, consent will be taken from the person providing initial KMC, which is expected to be the mother in most cases but may be another female family member or the father. If the mother later becomes available to provide KMC, she will be asked to provide informed consent for repeat swab samples at time of commencing skin-to-skin contact.

Figure 3. Flow chart for obtaining informed consent for neonatal participation in eKMC study



Obtaining the maternal/caregiver samples will not delay starting the intervention. For subjects allocated to the control group, informed consent for swab samples will be taken from the mother or caregiver prior to the subject receiving any skin-to-skin contact (table 3).

Table 3. Outline of consent process for mothers/caregivers providing biological samples

Study arm	Scenario	Consent taken from	Purpose of consent	Timing
Intervention	Mother present at time of recruitment	Mother	Recto-vaginal swabs Skin swabs	Before commencing intervention
	Another caregiver present at time of recruitment (E.g. Father/aunty/grandmother)	Caregiver who is present & providing skin-to-skin contact	Skin swabs	
		Mother once available	Recto-vaginal swabs Skin swabs	prior to starting skin-to-skin contact
Control	Mother present at time of recruitment	Mother	Recto-vaginal swabs Skin swabs	Before commencing any skin-to-skin contact
	Another caregiver present at time of recruitment (E.g. Father/aunty/grandmother)	No consent for biological samples taken. Wait for mother to be present or baby ready to start skin-to-skin contact with person other than mother	Skin swab	Before commencing any skin-to-skin contact
		Mother once available	Recto-vaginal swab Skin swab	As soon as possible after mother available and prior to starting any skin-to-skin contact

14.5.4 Special consent situations

If the mother of the baby is aged <18y old, she can still provide full informed consent, as per MRC Gambia SOP-CTS-015 section 4.8.7. If the caregiver has impaired mental capacity an alternative caregiver will be sought to provide consent instead. This could be the father of the baby or a trusted family member such as an aunty or grandmother.

14.5.5 General process of informed consent procedure

Study personnel will have undergone detailed training about informed consent procedures and only trained study personnel will take informed consent. All consent procedures will take place in a private, quiet area and every effort will be made to perform the informed consent process in a sensitive manner. Consent should not be taken on the neonatal unit, in-order to avoid distraction or distress to the caregiver.

The information sheet will be provided to the caregiver to read in English. If the care-giver is unable to read, the information sheet will be read out-loud in the presence of a literate and impartial witness, as per ICH-GCP guidance. Independent, impartial witnesses will be identified prior to the study starting and their curriculum vitae kept in the study file. They will be re-imbursed for expenses, in accordance with MRCG policy. If the caregiver does not speak English, the study personnel will translate the content of the information sheet into the language of understanding as applicable, as per standard practice at MRC.

The parent/caregiver will have the opportunity to have all questions answered before being asked to sign or thumb-print on the consent form. Written informed consent will be taken using the study information sheets and consent forms and all signed consent forms will be kept in a file in the locked study office at the study site for the duration of the study and later archived at MRCG with other study documents. Either a certified copy of the signed consent form or a second, signed form, will be given to the parent/caregiver. The research nurse or clinician will document that informed consent has been taken in the source medical record of the participant. A Statement of Guardianship form will be completed for all people giving consent who are not the parents of the participant.

If any photographs are taken involving study participants, informed consent will be taken prior to obtaining the image. This will be written consent, recorded on the MRCG Photographic consent form. Consent will be taken for use of the image in presentations, sensitisation and educational activities related to the research.

14.6 Participant confidentiality

Confidentiality will be ensured by the use of non-identifiable unique study numbers and exclusion of all subject identifiable information from the study database. The unique study number will be in the format N000. All paper and electronic data collection forms, laboratory forms, reports and administrative forms will include the study number and at least one other identifying detail (E.g. randomisation number, screening number, date of birth) As data will be collected on multiple occasions, a mastersheet linking the subject identifying information and the unique study number will be used to enable collection of data by different personnel at different time-points. The paired mother/caregiver will be allocated a unique study number in the format CG000 in a consecutive order. The caregiver enrolment log sheet will document the paired neonatal study number for each participant so that maternal/caregiver-neonatal dyads can be identified. The contact information will be kept within the participant folder and all forms will be kept in the locked study office at the study site.

15 FUTURE USE OF STORED SPECIMENS

All isolates identified from neonatal blood and CSF culture will be stored for future molecular characterisation and comparison with carriage and environmental isolates. All neonatal, maternal and environmental swab samples will be stored for future microbiological (culture, antibiotic sensitivity testing and ESBL detection) and molecular analysis (including 16SrRNA and whole genome sequencing), dependent on additional funding

16 FINANCING AND INSURANCE

This project is funded through a Wellcome Trust Research Training Fellowship to the PI and there is sufficient funding available for the study. Additional funding will be sought for future microbiological and molecular analysis of stored samples. London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

17 PUBLICATION / DISSEMINATION POLICY

The results of this study will be published in peer-reviewed scientific journals and as part of the PI's PhD thesis, through which potential users of the data will become aware of the data set.

The datasets collected will be available to other users once all relevant trial related publications in scientific journals have been accepted. Requests for access to the complete dataset will be reviewed by the Scientific Coordinating Committee of MRC Unit The Gambia and The Gambian Government/MRC Joint Ethics Committee to establish the validity of the request. The study documents and dataset will also be made available on LSHTM Data Compass repository.
The results will be made available to open-access databases once peer-reviewed publications have been accepted.
Local stakeholders will be informed of key results at an appropriate time following completion of the study.

18 REFERENCES

1. International Council for Harmonisation. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [Internet]. Geneva; 1995. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073087.pdf
2. Rosenberg RE, Ahmed AS, Saha SK, Chowdhury MA, Ahmed S, Law PA, Black RE, Santosham M, Darmstadt GL. Nosocomial sepsis risk score for preterm infants in low-resource settings. J Trop Pediatr. 2010 Apr;56(2):82-9.
3. World Health Organization. Thermal protection of the newborn: a practical guide [Internet]. Geneva: World Health Organization; 1997. Available from: http://apps.who.int/iris/bitstream/10665/63986/1/WHO_RHT_MSM_97.2.pdf
4. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME), 'Levels & Trends in Child Mortality: Report 2017, Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation', United Nations Children's Fund, New York, 2017
5. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, Lalli M, Bhutta Z, Barros AJ, Christian P, Mathers C, Cousens SN; Lancet Every Newborn Study Group. Every Newborn: progress, priorities, and potential beyond survival. *Lancet.* 2014 Jul 12;384(9938):189-20
6. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, Kinney M, Lawn J; Born Too Soon Preterm Birth Action Group. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10 Suppl 1:S2. doi: 10.1186/1742-4755-10-S1-S2.
7. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, Lawn JE, Cousens S, Mathers C, Black RE. Global, regional, and national causes of child mortality in 2000–15, an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet* 2016; 388 (10063):3027-3035
8. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, Ezzati M, Bhutta ZA, Marchant T, Willey BA, Adair L, Barros F, Baqui AH, Christian P, Fawzi W, Gonzalez R, Humphrey J, Huybregts L, Kolsteren P, Mongkolchati A, Mullany LC, Ndyomugyenyi R, Nien JK, Osrin D, Roberfroid D, Sania A, Schmiegelow C, Silveira MF, Tielsch J, Vaidya A, Velaphi SC, Victora CG, Watson-Jones D, Black RE, CHERG Small-for-Gestational-Age-Preterm Birth Working Group. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. *Lancet*. 2013 Aug 3; 382(9890):417-425
9. Blencowe H, Cousens S, Oestergaard M, Chou D, Moller AB, Narwal R, Adler A, Garcia CV, Rohde S, Say L, Lawn JE. National, regional and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012 June;379(9832): 2162-7
10. Okomo UA, Dibbasey T, Kassama K, Lawn JE, Zaman SM, Kampmann B, Howie SR, Bojang K. Neonatal admissions, quality of care and outcome: 4 years of inpatient audit data from The Gambia's teaching hospital. *Paediatr Int Child Health.* 2015 Aug;35(3):252-64
11. Oza S et al. Neonatal cause of death estimates for the early and late neonatal periods for 194 countries:2000-2013. Bull World Health Organ 2015;93:19–28
12. Kangaroo Mother Care: A Practical Guide. WHO. 2003

13. Charpak N, Ruiz-Peláez JG, Figueroa de C Z, Charpak Y. Kangaroo mother versus traditional care for newborn infants </=2000 grams: a randomized, controlled trial. Pediatrics. 1997 Oct;100(4):682-8.
14. Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database of Systematic Reviews 2016, Issue 8.
15. Lawn JE, Mwansa-Kambafwile J, Horta BL, Barros FC and Cousens S. Kangaroo mother care to prevent neonatal deaths due to preterm birth complications. *International Journal of Epidemiology* 2010; 39:i144–i154
16. Boundy EO, Dastjerdi R, Spiegelman D, Fawzi WW, Missmer SA, Lieberman E, Kajeepeta S, Wall S, Chan GJ. Kangaroo mother care and Neonatal outcomes: A meta-analysis. *Paediatrics* 2016 Jan;137(1)
17. Bergman NJ, Linley LL, Fawcus SR. Randomized Controlled Trial of skin-to-skin contact from birth versus conventional incubator for physiological stabilization in 1200-to 2199-gram newborns. Acta Paediatr. 2004 Jun;93(6):779-85.
18. Worku B, Kassie A. Kangaroo Mother Care: A randomized controlled trial on effectiveness of early Kangaroo Mother Care for the low birthweight infants in Addis Ababa, ethiopia. *J Trop Pediatr*. 2005;51(2):93-97
19. Vittner D, McGrath J, Robinson J, Lawhon G, Cusson R, Eisenfeld L, Walsh S, Young E, Cong X. Increase in Oxytocin From Skin-to-Skin Contact Enhances Development of Parent-Infant Relationship. Biol Res Nurs. 2017 Jan 1 [Epub ahead of print]
20. Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z. Hospital-acquired neonatal infections in developing countries. *Lancet* 2005 Mar;365(9465):1175-8
21. Hendricks-Muñoz KD, Xu J, Parikh HI, Xu P, Fettweis JM, Kim Y, Louie M, Buck GA, Thacker LR, Sheth NU. Skin-to-Skin Care and the Development of the Preterm Infant Oral Microbiome. Am J Perinatol. 2015 Nov;32(13):1205-16
22. Lorenz L, Dawson JA, Jones H, Jacobs SE, Cheong JL, Donath SM, Davis PG, Kamlin COF. Skin-to-skin care in preterm infants receiving respiratory support does not lead to physiological instability. Arch Dis Child Fetal Neonatal Ed. 2017 Jul;102(4):F339-F344. doi: 10.1136/archdischild-2016-311752. Epub 2017 Jan 17.
23. Wilman E, Megone C, Oliver S, Duley L, Gyte G, Wright JM. The ethical issues regarding consent to clinical trials with pre-term or sick neonates: a systematic review (framework synthesis) of the empirical research. Trials. 2015 Nov 4;16:502.
24. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2011;9(8):672–7.

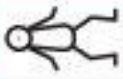
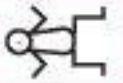
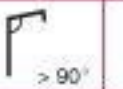
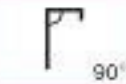
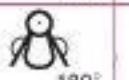
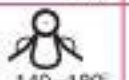
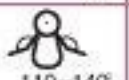
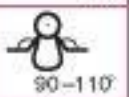
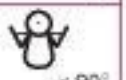
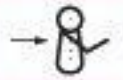
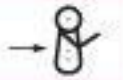
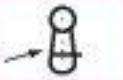
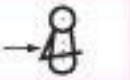
APPENDIX I. SCHEDULE OF RECRUITMENT ACTIVITIES

Activity	Tasks/method	Staff member	Documentation	Estimated time *
Identify potential participants	Screen all new admissions to EFSTH NNU to identify those with weight <2000g	MRC research nurse EFSTH nurse	Admission log	5 minutes
Sensitisation	Inform available parents/caregivers of potential participants about the study and screening procedures	MRC research nurse	eCRF	10 minutes
Screening for clinical eligibility	✓ Check age from source documents ✓ Weigh on study scale ✓ Examination ✓ Continuous pulse oximetry for 3h and manual recording of RR and breathing over 10 minute period at 00:00 & 02:50 ✓ Take temperature / blood glucose to aid clinical management	MRC research nurse	1. Screening log 2. Eligibility checklist with criteria 3. Screening Clinical Assessment Form	20 minutes 10 minutes OR 2h 50 minutes
Informed consent	Informed consent for eligible babies: - Consent for baby to participate in RCT - Consent to providing intervention if randomised to that arm	MRC research nurse/research Clinician	Information sheets & consent forms	40 minutes – 3h
Enrolment	Allocate unqiue study ID number to neonate and parent/caregiver	MRC research nurse	Enrolment logs	5 minutes
Collection of baseline data	✓ Auxiliary temperature ✓ Blood glucose ✓ Head circumference & length measurement	MRC research nurse	1. Clinical assessment form	30 minutes
	✓ Neonatal rectal, skin, & nasal swabs ✓ Maternal/caregiver paired swab samples (within 24h)		2. Biological samples log sheet 3. Transport log sheet	10 – 30 minutes
	Socio-demographic data		eCRF	60 minutes (as soon as possible)
Randomisation & allocation	Randomised & allocated to intervention or control arm	Research clinician	Randomisation log	10 minutes

* Screening, and enrolment activities are estimated to take between 2hr 20 minutes and 6h 10 minutes to complete (not including collection of socio-demographic data). If the informed consent process is delayed for any reason, this may be extended but the baby will be ineligible if no consent within 24h of admission.

APPENDIX II. NEW BALLARD SCORE FOR ASSESSING GESTATIONAL AGE

Neuromuscular Maturity

Score	–1	0	1	2	3	4	5
Posture							
Square window (wrist)	 > 90°	 90°	 60°	 45°	 30°	 0°	
Arm recoil		 180°	 140–180°	 110–140°	 90–110°	 < 90°	
Popliteal angle	 180°	 160°	 140°	 120°	 100°	 90°	 < 90°
Scarf sign							
Heel to ear							

Physical Maturity

Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink; visible veins	Superficial peeling and/or rash; few veins	Cracking, pale areas; rare veins	Parchment, deep cracking; no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40–50 mm: –1 < 40 mm: –2	> 50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/Ear	Lids fused loosely: –1 tightly: –2	Lids open; pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well curved pinna; soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals (female)	Clitoris prominent, labia flat	Clitoris prominent, small labia minora	Clitoris prominent, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Maturity Rating

Score	Weeks
–10	20
–5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

APPENDIX III: ADAPTED SCRIP SCORE FOR MEASUREMENT OF CARDIO-RESPIRATORY STABILITY OUTCOME

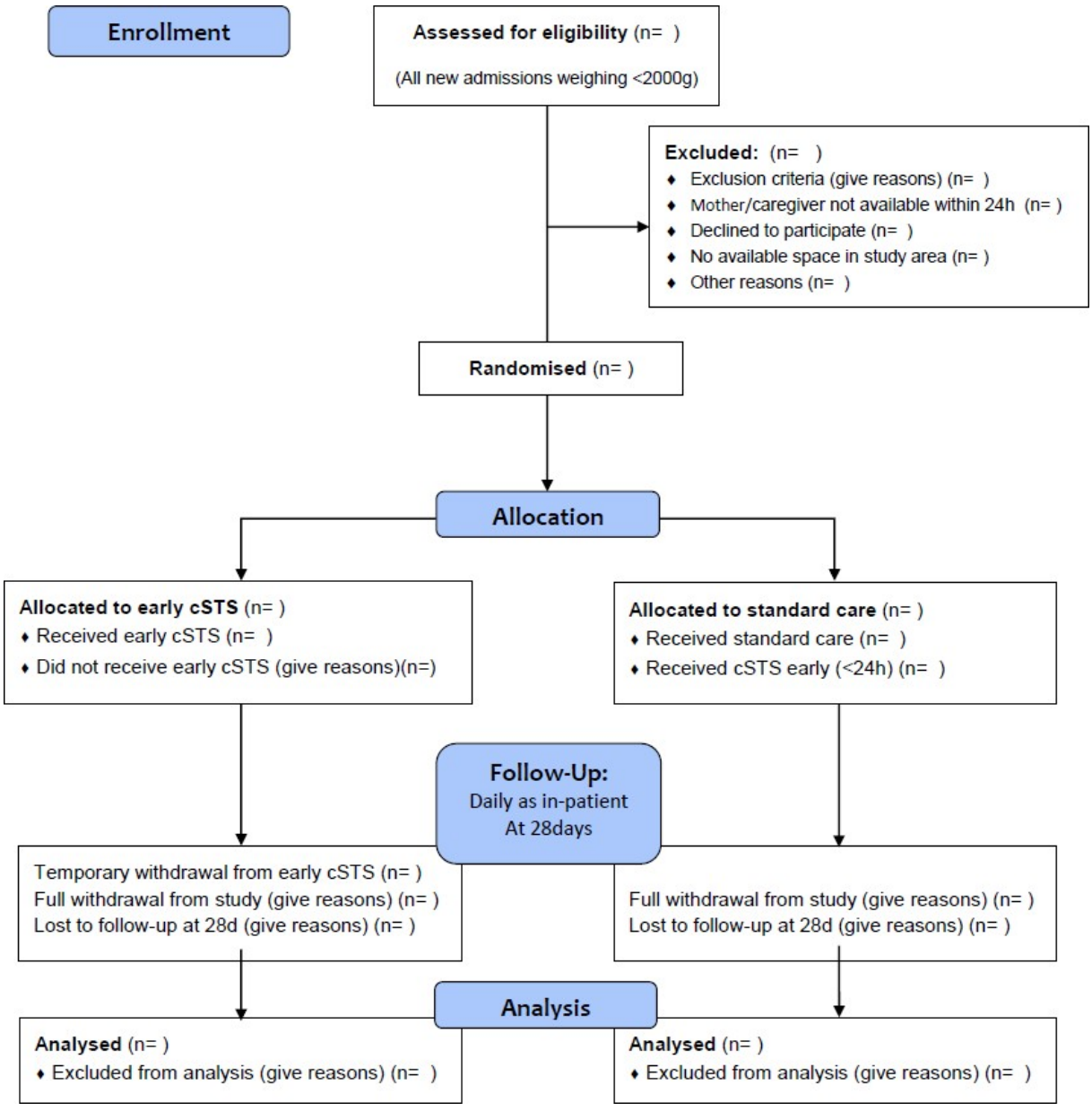
		2 points	1 point	0 points
A	**Cardiovascular stability**: Heart rate (beats per minute)	120 – 160 for 10 mins continuously	100 - 120 or 161 – 200 for >5 out of 10 mins	<100 or >200 continuously for >5 out of 10 mins
B	**Respiratory stability:** Breathing pattern and respiratory rate (RR) (breaths per minute)	Regular breathing And/or RR 20 – 60 continuously for 10 mins	Irregular or periodic breathing with 1 or more pauses for <10 secs And / or RR 20 – 29 or 61 – 100 for >5 out of 10 mins	Irregular breathing with 1 or more pauses for >10 secs And / or Irregular breathing with 1 or more pauses for <10 seconds but which result in oxygen saturation <88% Need for bag-valve-mask ventilation And / or RR <20 or >100 for >5 out of 10 mins
C	**Oxygen saturation (%)**	>88% continuously in room air for 10 mins	>88% continuously for >5 out of 10 mins in oxygen	<88% continuously for >5 out of 10 mins despite oxygen

Stable = 6

Mild – moderately unstable = 3 – 5

Severely unstable = 0 - 2

APPENDIX IV: TRIAL FLOW DIAGRAM. adapted from CONSORT guidelines, 2010[24]



APPENDIX V: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI, ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.