The OMWaNA Study: Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa: a multi-site randomised controlled trial to examine mortality impact in Uganda

Statistical Analysis Plan for Data and Safety Monitoring Board (DSMB)

Version 1.0, 08/12/2020

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1. Background

1.1 Background / rationale

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

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

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

2. Hypothesis and objectives

2.1 Aim

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

2.2 Hypothesis

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

2.3 Primary objective

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

2.4 Secondary objectives

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

3. Study methods

3.1 Protocol version

This analysis plan is based on the current version of the protocol: Version 2.1, 9 June 2020.

3.2 Study design

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

KMC is a package of care for preterm/LBW neonates consisting of: prolonged skin-to-skin contact; promotion of early & exclusive breast milk feeding; early hospital discharge with close follow up. Participants in the intervention arm will receive the continuous skin-to-skin contact aspect of KMC within 24h after birth and aiming for >18h / day. Participants in the control arm will be managed in incubators or radiant heaters, as per standard care, with intermittent then continuous skin-to-skin contact (KMC) started when clinically stable, as per standard care. KMC will be continued until hospital discharge and encouraged post-discharge until follow-up

If participants become unwell whilst receiving the intervention and fulfil the stopping criteria, then they will revert to standard care. The stopping criteria consist of the following:

- Severely unstable for >10 minutes, if:
    - SpO2 <88% in oxygen AND ≥1 of:
        - Respiratory rate <20 or > 100 breaths/min
        - Apnoea requiring bag-mask ventilation
        - HR <100 or >200 bpm
- Any other condition which precludes continuous skin-to-skin contact:
    - Severe jaundice requiring immediate management
    - Severe anaemia requiring blood transfusion
    - Active seizures
    - Severe abdominal distension
    - Omphalitis or infection of the umbilical cord
    - Apnoea requiring bag-valve-mask ventilation
    - Widespread skin infection of baby or caregiver providing skin-to-skin contact
    - Mother or caregiver not available or willing to do continuous skin-to-skin contact

Participants will re-commence skin-to-skin contact when the full stability criteria are met. The stability criteria are as follows:

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

A pragmatic study design will be used with a standardised preterm/LBW management protocol based on current standard care. All management will be provided by study site staff with input from research personnel on request.

3.3 Randomisation

Treatment allocation will be random and in a 1:1 ratio between groups. The random allocation sequence will be computer generated centrally at MRC/UVRI, and will use varying permuted blocks and stratified by birthweight (<1000, 1000-1499, or ≥1500g) and recruitment site. Participants who are of twin or triplet birth and result in completed twin admissions will be allocated to the same arm, according to the twin that was declared eligible first.

3.4 Sample size

Surveillance data collected on admissions to the Jinja Hospital neonatal unit between January and December 2016 (Perinatal Audit Data from Uganda Paediatric Association) suggest that the 7-day mortality rate in the control arm will be at least 25% across the four sites.

Assuming a control mortality rate of 25% across the 4 hospitals in our study, 1750 neonates (875 per arm) would enable us to detect a relative difference between arms of 22.4% (5.6% absolute difference) with 80% power and a significance level of 5%. If the control mortality rate were in fact as low as 18%, we would still be able to detect a relative difference of 27% (absolute difference of 4.8%). We plan to recruit 2188 neonates (1094 per arm) in order to allow for 10% withdrawal due to clinical deteriorations and consent withdrawal, and 10% dilution due to non-compliance and loss to follow-up. This sample size would enable us to detect absolute reductions of 6.3% and 5.4% from control rates of 25% and 18%, respectively, with 90% power.

4. Outcomes

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

The secondary outcomes are:

- Prevalence of hypothermia at 24 hours post-randomisation
- Mean duration of hospital admission (days and hours)
- Mean time from intervention/control procedures starting to exclusive breastmilk feeding (days and hours)
- Mortality within 28 days
- Time from intervention/control procedures starting to clinical stabilisation (days and hours)
- Time from intervention/control procedures starting to death (days and hours)

- Frequency of readmission
- Mean daily weight gain (g/day) at 28 days
- Infant-caregiver attachment at 28 days
- Women's well-being at 28 days

4.1 Timing of outcome assessments

Outcomes will be assessed according to the following schedule:

Timing	Outcome
24 hours	Hypothermia
7 days	Mortality
28 days	Mortality Time to death Frequency of readmission Mean daily weight gain Infant-caregiver attachment Women's well-being
Daily until hospital discharge (including day of discharge)	Exclusive breastfeeding Duration of hospital admission Time to clinical stabilisation

4.2 Timing of final analysis

All outcomes will be analysed collectively after the final participant has completed follow-up and data has been cleaned.

5. Trial datasets

5.1 Analysis levels

Statistical analysis will be carried out at the individual level.

5.2 Intention-to-treat dataset

The primary analysis will be carried out using the intention-to-treat dataset. Data will be analysed based on the participant according to the random allocation irrespective of whether the intervention was or was not entirely or partly taken up.

6. Study population

6.1 Trial flow chart

The number of participants included in enrolment, allocation, follow-up and analysis will be described as per CONSORT 2010 guidelines (Appendix 1, Figure 1). Reasons for exclusions, withdrawals and lost to follow-ups will be described, including number of consent refusals.

6.2 Screening data

The total number of neonatal admissions will be described for the study period.

6.3 Eligibility

The number of participants screened for eligibility and outcome of screening will be presented, including reasons for ineligibility. This will include the number and proportion of babies:

- Greater than 48 hours old at time of screening;
- Result of triplet (all three survived) or higher multifoetal pregnancy;
- Stable/ Indication for KMC 'certain' per WHO guidelines (defined as none of the following: oxygen, CPAP, IV fluids, therapeutic antibiotics or phenobarbital);
- Life-threatening instability (defined as SpO2 <88% and at least one of the following: respiratory rate <20 or >100 breaths/min, heart rate <100 or >200 beats/min, or apnoea requiring bag-mask ventilation);
- Has major congenital malformation, active seizures or severe jaundice requiring treatment;
- Parent/ Caregiver unable or unwilling to provide KMC or attend follow-up appointment;
- Parent/ Caregiver does not provide oral consent to screening for the trial;
- Parent/ Caregiver does not provide informed consent;
- No study bed available; and
- Any other reason.

6.4 Withdrawal / follow-up

The number and proportion of participants who temporarily or permanently withdraw from the intervention will be described. For temporary withdrawals, the number and proportion of those restarting the intervention at a later stage will be described. The number and proportion of participants who permanently withdraw from the study will be described with reasons for withdrawal. The proportion of participants who are followed up at 28 days will be described with further description of how many non-attenders were contacted by telephone and outcome (alive; died) ascertained.

Further details about consent and withdrawals can be found in Appendix 1, Table 1.

6.5 Baseline characteristics

Tabulation of demographic and other characteristics will be done using the intention-to-treat datasets. No significance tests will be performed to test for differences at baseline. Descriptive statistics for continuous variables will include the mean, standard deviation, median, interquartile range and the number of observations. Categorical variables will be presented as numbers and percentages. Analysis will be performed with number of participants in each arm as the denominator. No significance tests will be performed to test for differences at baseline.

Baseline characteristics of mothers and babies will be tabulated by treatment arm (Appendix 1, Tables 2 and 3).

7. Protocol adherence

Adherence to the intervention will be monitored with daily amount of time spent in skin-to-skin position. Adherence will be defined as follows:

- For the intervention, the skin-to-skin contact aspect of KMC should commence within 24 hours of randomisation. The target is an average of 18 hours per day but it is recognised that this will be difficult to achieve.

- For standard care, skin-to-skin contact should commence 24 hours after meeting the stability criteria. Duration for the skin-to-skin contact aspect of KMC will be recorded.

Data on actual management will be collected in both arms of the trial. Deviations from the randomised treatment will be noted and tabulated (Appendix 1, Tables 4 and 5).

8. Analysis

8.1 Statistical software

STATA Version 16 will be used for analysis.

8.2 Methods

8.2.1 Primary analysis

We will report risk ratios for mortality within 7 days (primary outcome) and 28 days (secondary outcome) for intervention versus control with associated 95% confidence intervals (CI). Time from intervention/control procedures starting to death, time from intervention/control procedures starting to exclusive breastmilk feeding, and length of stay will be analysed using Kaplan-Meier plots and hazard ratios, with accompanying 95% CI calculated using Cox proportional hazards regression. All other secondary outcomes will be analysed using appropriate regression models accounting for the nature of the distribution of the outcome, and results will be presented as appropriate effect sizes with a measure of precision (95% CI). Both unadjusted analyses and analyses adjusted for stratification factors will be carried out. Robust standard errors will be used to account for clustering of outcomes within completed twin participants.

8.2.2 Subgroup analysis

Subgroup analyses are planned to explore between-group difference in the impact of KMC compared to standard of care on mortality, by gestational age (<28, 28-<33, or ≥33 weeks), birthweight (<1000, 1000-1499, or ≥1500g), hospital site, level of predicted mortality risk based on the NMR-2000 score [high (≤16), medium (17-22), low (≥23)], time of initiation (<12, 12-<24, or ≥24 hours) and continuity of KMC (median hours per day: <6, 6-<12, 12-<18, or 18-24 hours). The relative measures of effect within each of these subgroups will be estimated with a test of interaction (reported as p value and 95% confidence interval).

9. Statistical and Analytical Issues

9.1 Adjustments for potential covariates

The primary analysis will be carried out that include adjustment for stratification factors. Secondary analyses will be carried out that include adjustment for sex and age. Additional exploratory analyses will control for any baseline measures that appear to be imbalanced between arms.

9.2 Sensitivity analyses

Sensitivity analyses regarding missing data such as best- and worst-case scenario may be conducted for the primary outcomes.

9.3 Dose-Response analysis

In addition to the subgroup analysis of continuity of KMC, a full dose-response analysis will be carried to explore the impact of the duration of KMC on primary outcome.

9.4 Dropouts and Missing data

The data coordinating centre at MRC/UVRI will be responsible for reviewing all data as they arrive and contacting the centres about any missing data. Missing data will be chased until received, confirmed as not available, or the trial is at the analysis stage. Data quality, follow-up and trial monitoring will be facilitated through the development of a trial REDCap database, including validation, verification, monitoring and compliance reports and follow-up report functionalities.

Only a small amount of missing data is expected and it is not thought likely that it will have to be accounted for in any analysis. We would consider using inverse probability weighting if missing data were larger than expected and/or there was differential attrition between the trial arms. We would also attempt ensure that the reason for the differential attrition was fully understood. Sensitivity analyses (as detailed above) will however be conducted for the primary outcomes.

9.5 Outliers

Any unusual values/potential outliers will be queried. If the value is found to be correct, then it will be included in all analyses.

9.6 Statistical interim analyses and stopping guidance

An independent Data Safety and Monitoring Board (DSMB) will be establish before the start of the trial. The DSMB will meet and review, with strict confidence, the trial data approximately every 6 months and at least yearly for the duration of the trial. The Chair of the DSMB may also request additional meetings/analyses.

A formal interim analysis will be performed on the primary outcome when approximately half of neonates have been randomised (around 1 year into the trial). An earlier interim analysis may be carried out if requested by the Chair of the DSMB. The DSMB will have access to all data. An independent statistician will perform the interim analysis and report to the DSMB. In the light of these data and other evidence from relevant studies, the DSMB will inform the Trial Steering Committee (TSC) if in their view:

i. It is evident that no clear outcome will be obtained with the current trial design.
ii. They have a major ethical or safety concern.
iii. It is evident that the intervention is clearly superior and continuing the trial would be unethical to those in the control arm.

The DSMB have agreed to the following stopping rules:

- Efficacy – the DSMB will recommend stopping the trial if there is evidence that the intervention (KMC) is better than the control (standard care) with a p-value of <0.001 for the primary outcome (Peto-Haybittle).
- Futility – the DSMB will review the available evidence and recommend stopping the trial, for example, if there is insufficient evidence that the intervention (KMC) is more effective than the control (standard care). Assessment of futility will also consider recruitment rates and the results from the WHO i-KMC trial at the time of the interim analysis.
- Harm – the DSMB will regularly monitor for safety and recommend stopping the trial accordingly.

9.7 Multiple Comparisons/Multiplicity

The number of secondary outcomes that will be tested for significant differences between arms is small and thus no formal adjustment for multiple comparisons will be made.

10. Safety monitoring

Information on adverse events, serious adverse events (SAEs) and deaths will be collected and reported in both arms of the trial (Appendix 1, Table 8). The DSMB will receive a summary of SAEs after 1 month of recruitment, then move to three- or six-monthly; the DSMB will decide the frequency following the first report. The DSMB will note these and, unless there is a special cause of concern, will consider them as part of the planned DSMB meetings which will discuss interim analyses. All SAEs will also be reported to the Sponsor and ethical review committees (MRC/UVRI and LSHTM) as part of their respective annual progress and safety report.

Full details on Adverse Events and Safety Reporting are given in the trial protocol and Adverse Event Reporting SOP.

Appendix

Appendix 1: Dummy Tables for OMWaNA DSMB Reports

References

Trial Protocol

SOP 012: Standardised preterm/LBW Management Protocol

SOP 010: Adverse Event Reporting