Statistical Analysis Plan

STUDY TITLE	Innovative Management PRactices to Enhance hoSpital quality and Save lives in Malawi (IMPRESS) A cluster-randomised trial of the impact of a multi-faceted hospital management intervention on in-hospital mortality and the quality of clinical care for small and sick newborns
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Abbreviations

CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
DE	Design Effect
KMC	Kangaroo Mother Care
KuHES	Kamuzu University of Health Sciences
LSHTM	London School of Hygiene & Tropical Medicine
ODK	Open Data Kit
OR	Odds Ratio
NID	Neonatal Inpatient Data
REDCap	Research Electronic Data Capture
WHO	World Health Organisation

Introduction

Background

As with many countries in sub-Saharan Africa neonatal mortality in Malawi remains high (23 per 1,000 live births).

Malawi is a founding member of WHO's Quality of Care Network and has committed to halving deaths for inpatient neonates in five years. There has been a long-term focus on improving quality of care at birth and now there is a new focus on small and sick newborn care. The government package to address this target population is NEST360 which started in 2019 and seeks to implement a set of clinical interventions: provision of affordable technologies to keep babies warm, help them breath, treat jaundice and control infections; and training of technicians and clinicians.

However, the clinical care setting also depends on factors at the organisational level, as exemplified by common problems such as drug stock-outs, staff absenteeism, and power outages. Improving management practices – so that hospitals effectively manage staff, drugs and medical supplies, have sound financial management and are data-driven in their decisions – could plausibly improve quality of care.

The IMPRESS project aims to improve clinical care by improving hospital management practices. The project comprises two phases: a formative phase of research on hospital management followed by the co-design and evaluation of a hospital management intervention. This statistical analysis plan covers only the trial.

This project builds on, and adds value to NEST360. Most pertinently, we will use a prospective de-identified individual level newborn admissions dataset, first setup by NEST360 and now integrated into the routine data collection systems of hospitals.

Study Objectives

The aim of the research is to examine whether enhanced management practices can improve health outcomes and clinical quality for small and sick newborns in hospitals. A multi-disciplinary team from KUHeS and LSHTM will address the following interlinked objectives:

1. Evaluate effectiveness of the intervention on neonatal mortality through a cluster randomised trial;
2. Evaluate effectiveness of the intervention on the quality of clinical care and secondary outcomes through a cluster randomised trial;
3. Assess the intervention's acceptability, fidelity, and mechanisms through multi-methods research and estimate its cost-effectiveness.

Study Design

Overview

The cluster-randomized trial is being conducted in 30 hospitals in Malawi.

The study hospitals (intervention and control hospitals) all participate in NEST360 – they receive a bundle of inputs and activities that include: the provision of affordable technologies to keep babies warm, help them breath, treat jaundice and control infections; the training of technicians and clinicians; enhanced data systems; and support for regular quality improvement visits.

There are two study arms. Hospitals in the intervention arm receive a multi-faceted management intervention in addition to the existing NEST360 activities (10 hospitals). Hospitals in the control arm receive the existing NEST360 activities (20 hospitals).

The primary outcome, all cause in-hospital mortality, will be assessed in the entire population of newborns admitted to the neonatal unit of the 30 study hospitals. This will be done by analysing the Neonatal Inpatient Dataset, a routine patient level information system established by NEST360 that captures clinical data on all neonatal unit admissions.

The trial intervention was delivered over a 1-year period from 19 June 2023 to 30 June 2024.

Intervention

The study intervention comprises multiple components that were developed through a co-design process, which included a series of intervention design workshops with hospital managers and health workers, central level experts, and other stakeholders in Malawi.

Core components of the intervention

The intervention comprises technical assistant teams that visit each hospital for one week every month over a year period. Each team is made up of two technical assistants, who have health care management post-graduate qualifications and experience. The technical assistant teams support hospitals to adopt priority management practices that are critical for the delivery of high-quality care for small and sick newborns. More specifically, the multi-faceted intervention includes six core components:

1) Situation analysis and management implementation plan. This analysis is based on data from the baseline hospital management survey and the Neonatal Inpatient Data dataset. The management implementation plan describes for a set of priority management practices the activities that the hospital will implement during the course of the intervention to strengthen the practice. Each practice is explicitly linked to a clinical area.

2) Monitoring adoption of management practices. Key management practices indicators are monitored at bi-monthly intervals. Targets are set by hospital staff at the beginning of the intervention.

3) Data for action. Feedback on the adoption of management practices is provided through dashboards, and recognition awards are awarded every two months to the best improvers.

4) Small tests of change. Changes are implemented in a cyclical fashion using small tests of change before taking changes system-wide. A key part of this component is support to the functioning of the Quality Improvement Support Team (QIST) and Work Improvement Team (WIT).

5) Hospital peer-to-peer learning. Staff from well-performing hospitals share best practice and act as coaches in collaborative learning sessions.

6) Coaching on management. Training modules are made available to respond flexibly to the needs of individual hospitals.

Support components

These core components are accompanied by several support strategies. These include: 1) identifying individuals who dedicate themselves to supporting and driving through implementation, and 2) meetings with the hospital leadership to encourage commitment to quality improvement and 3) facilitating better communication between clinicians and managers.

Target of intervention

The intervention targets middle managers in the hospital and health staff in the neonatal unit. A secondary target of the intervention is the hospital leadership. In terms of institutional

structures within the hospital, the primary focus is the Quality Improvement Support Team at the hospital level and the Work Improvement Team at the neonatal unit level.

Duration of implementation

12 months

Phases of implementation

The management intervention is comprised of two phases. The first is a diagnostic phase over the first two months involving the first two components of the intervention. The second is an implementation phase involving the other components (month 3 to month 12). The original design envisaged a third phase in the last four months of the intervention during which support and the frequency of hospital visits would be tapered. However, this third phase was not initiated to maintain the intensity of the intervention throughout the implementation phase.

Table: Timeline of intervention roll-out and measurement of outcomes

Calendar date	Dec22-Mar23	Apr-Jun 2023	Jly-Sep 2023	Oct-Dec 2023	Jan-Mar 2024	Apr-Jun 2024	Jly-Sep 2024	Oct-Dec 2024	Jan-Mar 2025
Month of intervention			1-3	4-6	7-9	10-12			
Management intervention									
Co-design and hospital sensitisation									
Phase 1 (components 1 & 2)									
Phase 2 (components 3 to 6)									
Outcomes measurement									
Baseline mortality (NID)									
1ry outcome – mortality (NID)									
2ry outcomes – clinical quality (NID)									
2ry outcomes – management score survey									
Analysis and reporting									

Notes:

1. Baseline period 19 Dec 2022 – 19 Jun 2023
2. Endline period 1 Apr 2024 – 30 Sept 2024
3. Matching done using mortality data (NID) from 1 Oct 2021 – 30 Sept 2022
4. A baseline management survey was conducted in Mar/Apr 2022

Inclusion-Exclusion Criteria

In the analysis, we will implicitly apply the following inclusion criteria:

- Baby admitted to the neonatal unit of a study hospital
- Baby alive at admission to the neonatal unit
- Admission to the neonatal unit is recorded

In addition, we have chosen to apply the following exclusion criterion:

- Birthweight of baby is 1000g or less or is not recorded

Babies with a birthweight of 1000g or less are excluded for two main reasons. First, we do not expect the intervention to deliver benefits to this vulnerable group because of the clinical constraints of our context. Secondly, there are concerns of missing data for babies with very low birthweight as birthweight is often not recorded among very low birthweight babies.

Randomisation and Blinding

Randomisation

Hospitals were assigned to intervention or control in a ratio of 1:2 using stratified randomization (10 intervention hospitals versus 20 control hospitals).

The stratification was done by grouping hospitals into 10 mortality strata of 3 hospitals each, based on the incidence of neonatal mortality in the period 1 Oct 2021 to 30 Sep 2022. That is the 3 hospitals with the lowest mortality formed the first stratum, the 3 hospitals with the next lowest mortality formed the second stratum and so on. Stratification ensures that the average neonatal mortality rate is similar in two study arms.

Hospitals were allocated to intervention or control using a computer-generated randomisation list that was generated by the trial statistician. Study hospitals were informed of intervention assignment through a mixture of in-person site visits and Zoom calls.

Blinding

Due to the nature of the intervention, it was not possible to blind study hospitals to the intervention after assignment.

Sample Size

The sample size calculations were based on the randomisation of 30 hospitals (10 intervention hospitals and 20 control hospitals), and account for the method of randomisation, i.e., stratification on baseline mortality.

We estimated the study power via a design effect calculation to account for three features of the design: 1) cluster randomisation 2) variable cluster sizes and 3) matching (Rutterford, 2015). The design effect corresponds to the factor by which the sample size must be inflated to achieve the same power as in an individually randomised study. To implement the design effect calculation we calculated separate design effects for the effects of clustering (DE1), variable cluster size (DE2) and matching (DE3) and multiplied these to generate the overall

design effect (i.e., overall DE = DE1×D2 ×D3). Note that DE1>1 and DE2>1, and therefore increase the overall DE, while DE3<1 and therefore decreases it.

After calculating the design effect, we estimated the study power by translating the study sample size into an effective sample size for an equivalent individually randomised trial. We then used the function pwr.2p2n.test() from the R package "pwr" to compute the power from the effective sample size.

Table 1. Parameter values

	Symbol	Value
Proportion of deaths among admission in control arm		0.13
Relative risk	RR	0.80
Mean cluster size (no. neonatal admissions)	m	450
Coefficient of variation of cluster sizes	CV	0.7
Intra cluster correlation	ρ	0.01
Correlation within strata (matched triplets)	ρ_x	0.4

The parameter values for the sample size calculation were estimated from data on neonatal admissions and mortality in study hospitals between 1 Jul 2021 – 30 June 2022. Note that the sample size calculation was done prior to the matching and hence used data from a slightly earlier period. Admissions ≤1000g were excluded.

The intra-cluster correlation, ρ, was calculated from an estimate of between-hospital variance obtained by fitting a random effects logistic regression, without covariates and with hospital as the random effect, to the data on neonatal morality.

The correlation within matched triplets, ρ_x, was estimated in four steps:

1) the data were split into two six-month periods (baseline period: 1 Jul – 31 Dec 2021, follow up period 1 Jan – 30 Jun 2022);

2) matched triplets were created using data from the baseline period;

3) the correlation between randomly selected pairs within the matched triplets was calculated using data from the follow up period;

4) the random selection in 3) was repeated multiple times (n=100) and the average correlation was computed.

Table 2. Sample size calculations

p0	p1	RR	ρ	ρ_x	CV	m	DE1	DE2	DE3	DE	power

0.13	0.098	0.75	0.007	0.4	0.7	450	4.14	1.1	0.6	2.73	0.93
0.13	0.104	0.8	0.007	0.4	0.7	450	4.14	1.1	0.6	2.73	0.77
0.13	0.111	0.85	0.007	0.4	0.7	450	4.14	1.1	0.6	2.73	0.51

Assuming 450 admissions per hospital, which equates to six months of follow up, and 13% mortality in control clusters, we estimated that the study design provides 77% power to detect a 20% reduction in morality in the intervention clusters and 93% power to detect a 25% reduction.

Data Storage

Neonatal Inpatient Dataset

The Neonatal Inpatient Dataset is stored in a REDCap database. The server is maintained by the NEST360 designated country partner and backed up regularly. The IMPRESS study team has access to de-identified patient level data in the Neonatal Inpatient Dataset, as formalised in a data sharing agreement between the Ministry of Health and KUHeS

Hospital Management Survey

Data from the hospital management surveys is stored in an ODK database on a secure KUHeS server, where the data can be accessed only by the IMPRESS data manager. Only de-identified data from the interviews with hospital managers will be shared with other IMPRESS researchers. Hospital management data contain hospital identifiers to allow them to be linked with data from other sources, such as the Neonatal Inpatient Dataset. However, data will only be presented in aggregate form in the dissemination of findings such that individual hospitals are not identified.

Further information on the datasets and data management procedures is provided in the study protocol.

Analysis Cohort

The analysis cohort will consist of neonatal admissions at the n=30 study facilities with data in the NID dataset.

It will further be restricted to:

- Newborns with birthweight of more than 1,000g (newborns missing birthweight will be excluded)
- Newborns admitted from month 10 and up to and including month 15 after the start of intervention implementation (1 Apr – 30 Sep 2024)
- Newborns with known survival status at discharge (newborns missing date of admissions or date of discharge/death will be excluded)

A flow chart will be produced to describe exclusions from the analysis cohort.

Note that any admissions during the study period that have not been discharged by the time of the final data download will be missing data on survival status at discharge and will consequently be excluded from the final analysis. However, we expect the number of such cases to be minimal, as the final data download occurs three months after the study period ends (see below), and there are very few admissions with a length of stay exceeding three months.

Study Variables

Primary outcome

- All-cause neonatal mortality

All-cause neonatal mortality will be defined as death from any cause occurring from day 0 up to and including day 27 of life. Deaths will be identified using the discharge status variable (in_dis_stat), and the date of discharge or death will be used to determine whether the death occurs within 28 days of admission. We will assume that newborns discharged alive before day 28 survive until day 28.

The denominator will be the total number of admissions, meaning the same newborn may be counted more than once in the unlikely event that they are readmitted. Note that it is not possible to use the number of newborns as the denominator due to the lack of a unique identifier.

Secondary clinical outcomes (denominator = entire analysis cohort)

- Pulse oximetry done at admission
- Temperature taken at admission
- Glucose test done at admission
- All three diagnostics done at admission (pulse oximetry, temperature taken, glucose test completed)
- Exclusively breastfed at discharge from the neonatal unit (or death)

Secondary clinical outcomes (denominator = subgroup of analysis cohort)

- Receipt of antibiotics during admission among newborns with a clinical sepsis diagnosis
- Absence of hypothermia (<36.5°C) at admission
- Kangaroo Mother Care (KMC) during admission among newborns with low birthweight (<2500g)
- Receipt of bilirubin test during admission among newborns presenting with jaundice at admission
- Receipt of phototherapy during admission among newborns presenting with jaundice or who had a bilirubin test done during admission
- Blood culture done during admission among newborns given antibiotics
- Blood culture done during admission among newborns with a clinical diagnosis of sepsis
- Receipt of Continuous Positive Airway Pressure (CPAP) among neonates meeting the criteria for CPAP

- Cause-specific mortality (categories: congenital malformations, prematurity, infection, intra-partum related, jaundice)

Criteria for CPAP:

1) Birthweight 1000g-1499g OR
2) Birthweight 1500g-1999g AND respiratory distress syndrome AND hypoxia (oxygen saturation <90%)

Secondary outcomes related to management and experience of care:

- Mean number of neonatal unit admissions per month
- Hospital management quality score, measured 14-15 months after the start of the management intervention through the Hospital Management Tool
- Hospital management records score, measured 14-15 months after the start of the management intervention through the Record Review Tool
- Experience of care score calculated from the Experience of Care Survey

Each hospital's overall management score will be determined by averaging scores across 28 management practices, with each practice rated from 1 to 5. Consequently, the overall score will also range from 1 to 5. In addition we will calculate a standardised score (Z-score) for each hospital by subtracting the overall mean and dividing by the standard deviation.

Similarly, the overall record review will be calculated by averaging scores for 26 items, with each item scored 1 if present and 0 if not. Thus the overall record review score represents the proportion of items present.

An experience of care score will be calculated for each hospital using data from the Experience of Care Survey. The survey will involve interviewing a sample of mothers whose babies are admitted at study hospitals. Although currently under development it is likely to include questions on: participation and involvement, access to care, emotional support, newborn comfort, evaluation of health services and general satisfaction.

Table: Key variables in NID (mw_IMPRESS_Request_Jan2022_to_Sep2024_17022025.dta) and variables added to dataset (shown in italics)

Variable	Description	Categories
alloc	*Allocation of hospitals to trial arms*	*control* | *treatment*
strata	*Randomisation strata*	
in_doa	Date of Admission:	
in_dob	Date of Birth (DOB):	
analysis_cohort	*Included in baseline or endline cohort or reason for exclusion*	excluded: non-study hospital | excluded: admission not during baseline or endline periods | excluded: missing dob or dob < date discharge | excluded: missing birth weight | excluded: birth weight <=1000g |excluded: date of discharge/death missing |excluded: discharge status missing | baseline | endline

analysis_cohort_bwt_imp	Variable similar to *analysis_cohort but with classification based on imputed birthweight*	
in_sex	Newborn Sex:	1, Male|2, Female|3, Indeterminate|-1, Not recorded|-3, Not readable
sex	*Newborn Sex:*	*1, Male/0, Female*
in_delmode	Mode of Delivery:	1, Normal vertex|2, Forceps|3, Vacuum extraction|4, Vaginal breech|5, Caesarean delivery (C-section)|-1, Not recorded|-3, Not readable
delmod	*Mode of Delivery:*	*1, "Vaginal" / 2, "Caesarean"*
in_hiv_mstat	Maternal HIV Status:	0, Negative|-2, Unknown|1, Positive|-1, Not recorded|-3, Not readable
hiv	*Maternal HIV Status:*	*0, Negative/1, Positive*
in_m_age	Maternal Age (Years):	
in_m_age_cat	*Maternal Age (Years):*	*<20 | 20-29 | 30-39 | 40+*
singleton	*Number of babies born to mother*	*0, Multiple | 1, Singleton*
month_adm	*Month of admission*	
age_adm	*Age at admission (days)*	
age_adm_cat	*Age at admission (categories)*	*0 days |1-3 days |4-6 days |7-28 days*
in_admwt	Weight on admission (grams)	
in_bwt	Birth weight (grams)	
In_bwt_cat	*Birth weight (grams): categories*	*<=1000g | 1001-1499g | 1500-1999g | 2000-2499g | 2500-3999 | 4000+*
in_bwt_imp	*Birth weight (grams). (with birthweight imputation – see sensitivity analysis 2)*	
in_dis_dod	Date of Discharge/Absconded/Death:	
in_dis_stat	Newborn status at discharge:	0, Dead|1, Alive|-1, Not recorded|-3, Not readable
los	*Length of hospital stay (days)*	
d28mort	*Newborn day 28 survival status*	*0, Alive|1, Dead*
in_admreas_1 in_admreas_2 in_admreas_3	Reason for Admission (first, second, third)	1, Congenital Malformation (Neonatal working diagnosis) | 3, Small Baby / Preterm / Low Birthweight (Neonatal working diagnosis) | 2, "Birth asphyxia"/ Birth Injury (Neonatal working diagnosis) | 19, Suspected Infection - sepsis/meningitis (Neonatal working diagnosis) | 20, Tetanus (Neonatal working diagnosis) | 5, Respiratory Distress/Difficulty in Breathing (Danger signs) | 6, Convulsions (Danger signs) | 7, Temperature too high (Danger signs) | 8, Temperature too low (Danger signs) | 9, Jaundice (Danger signs) | 10, Vomiting (Danger signs) | 11, Pallor/Severe Anaemia (Danger signs) | 12, Cord red/sticky (Danger signs) | 13, Not feeding/Failure to suck (Danger signs) | 4, Large Baby (Neonatal reasons) | 21, PROM and Maternal Fever (Maternal reasons) | 22, Other (Maternal reasons) | 16, Other (None of the above) - Specify | 17, Not Recorded / No Reason For Admission | 18, Not Readable
adm_diag	*Admission diagnosis*	*1,Congenital malformation| 2, Birth asphyxia| 3, Small baby/preterm/low birth*

		weight |4, Respiratory distress/difficulty breathing| 5, Suspected infection| 6, Other
in_abx_admin	Were antibiotics administered?	1, Yes|0, No|-1, Not recorded|-3, Not readable
in_bloc	Birth Location:	1, Inborn (born at this facility)|2, Outborn (born outside this facility)| *-1, Not recorded|*-3, Not readable **Recoded to missing (.) after cleaning*
inborn	*Birth Location:*	*0 Outborn (born outside this facility)| 1 Inborn (born at this facility)*
in_tmp_adm_cel	Temperature on admission (&#176C):	
in_o2_lo	Lowest recorded oxygen saturation (%):	
in_o2_satur_adm_doc	Was oxygen saturation (%) recorded on admission?	1, Yes|0, No|-1*, Not recorded|-3*, Not readable **Recoded to missing (.) after cleaning*
in_tmp_adm_doc	Was temperature recorded on admission?	1, Yes|0, No|-1*, Not recorded|-3*, Not readable **Recoded to missing (.) after cleaning*
in_glu_adm_doc	Was blood sugar recorded on admission?	1, Yes|0, No|-1*, Not recorded|-3*, Not readable **Recoded to missing (.) after cleaning*
in_o2tmpglu_adm_doc	*Were all 3 diagnostics recorded at admission?*	*1, Yes|0, No*
in_fed_dis	Feeding at discharge	1, Exclusive breastmilk|2, Formula only|3, Fortified breastmilk|4, Predominant breastmilk|5, Combination of breastmilk and formula|6, Unknown - Absconder|-1, Not recorded|-3, Not readable
in_fed_dis_bin	*Was the newborn exclusively breastfed on discharge from the neonatal unit?*	*1, Yes|0, No*
nohypothermia	*Absence of hypothermia*	*1, Yes|0, No*
in_kmc_admin	KMC Administered:	1, Yes|0, No|-1, Not recorded|-3, Not readable
in_bil_doc	Was bilirubin tested?	1, Yes|0, No|-1, Not recorded|-3, Not readable
in_pt_admin	Was Phototherapy Administered?	1, Yes|0, No|-1, Not recorded|-3, Not readable
in_bld_doc	Blood culture for suspected sepsis:	0, Not Done|1, Done - Culture Negative|2, Done - Culture Positive|3, Done but Unknown Result|-3, Not readable
in_cp_admin	CPAP Administered:	1, Yes|0, No|-1, Not recorded|-3, Not readable
cp_admin_elig	*CPAP administered to those in need*	*1, Yes|0, No*
abx_admin	*Antibiotics given among clinical sepsis cases (suspected sepsis/meningitis, probable sepsis, culture-positive sepsis, probable meningitis, culture-positive meningitis, pneumonia, other infection, infection (unspecified))*	*1, Yes|0, No*
bld_done_abx	*Blood culture done in newborns receiving antibiotics*	*1, Yes|0, No*
bld_done_inf	*Blood culture done in suspected cases of sepsis*	*1, Yes|0, No*
in_kmc_admin_in_bwt	*KMC in newborns with low birth weight*	*1, Yes|0, No*
in_kmc_admin_in_bwt_imp	*KMC in newborns with low birth weight or imputed low birth weight*	*1, Yes|0, No*
in_bil_doc_jaundice	*Bilirubin test done for jaundice*	*1, Yes|0, No*
in_pt_admin_jaundice	*Phototherapy done for jaundice*	*1, Yes|0, No*
in_dx_prim_1	Primary Category (1):	1, Congenital Malformations|2, Prematurity|3, Infection|4, Intrapartum-related|5, Jaundice (Pathological) |6, Other

		(None of Above)|-1, Primary Cause/Final Diagnosis Not Recorded (No Details To Enable Death Certification)|-3, Not Readable
in_dx_prim_if_1 in_dx_prim_if_2 in_dx_prim_if_3	Sub-Categories of Infection (first, second and third)	1, Probable Sepsis|2, Culture-Positive Sepsis|3, Probable Meningitis|4, Culture-Positive Meningitis|5, Pneumonia|6, Tetanus|7, SARS-CoV-2 (COVID-19)|8, Other Infection|9, Infection Cause But Not Able to Specify
in_dx_prim_prem_1	Sub-Categories of Prematurity:	1, Respiratory Distress Syndrome (of Prematurity)|2, Intraventricular Haemorrhage|3, Necrotizing Enterocolitis|4, Other Prematurity|5, Prematurity Cause But Not Able to Specify
in_rds	Signs of severe respiratory distress (e.g. severe in-drawing, grunting, high respiratory rate (>80 breaths)):	1, Yes|0, No|-1, Not recorded|-3, Not readable
cod	*Cause of death*	*0, Alive at discharge /1, Congenital malformation/2, Prematurity/3, Infection/4, Intrapartum related/5, Jaundice/6, Other*

Interim Analyses and Timing of Final Analysis

Interim analyses will be conducted for DSMC meetings. At these meetings, we will present monthly rates of neonatal mortality for each of the study hospitals as the primary signal of safety, and monthly numbers of admissions to assess delays in data entry. Missing data in key study variables, such as birthweight, sex will also be assessed at these meetings.

The final analysis will use data from the period 1 April – 30 Sept 2024. Allowing for a 3-month delay in data entry, it is anticipated that the data for the final analysis will be download in Jan 2025 and analysed during the period Jan – Mar 2025.

Data for the final analysis will not be downloaded until the statistical analysis plan has been approved by the IMPRESS DSMC and trial management group.

Subgroup Analyses

Analyses will be presented for all neonatal admissions and separately for admissions in the following subgroups.

Birthweight

- 1001g-1500g
- 1501g-2000g
- 2001g-2500g
- 2501g+

Sex

- Male
- Female

Place of birth

- Inborn
- Outborn

Period

- Late implementation (1 April – 30 June, 2024)
- Post implementation (1 July – 30 Sept, 2024)

Statistical Considerations

Descriptive Analysis of Participants

We will describe the admissions included in the analysis using a flow diagram (Figure 1).

Baseline characteristics of the admissions and hospital-level characteristics will be compared between study arms. Specifically, we will compare the following variables between arms:

- Sex
- Age at admission
- Birthweight
- Maternal age
- Mode of delivery
- Maternal HIV status
- Number of monthly admissions
- Baseline mortality per 100 admissions
- Length of stay
- Place of delivery (inborn/outborn)
- Diagnosis at admission

The categorisation of the variables is shown in Table 1. For continuous variables, we will present the median and interquartile range (IQR).

Characteristics of the Intervention

The description of the intervention will adhere to the TIDieR guidelines TIDieR Checklist.

We will use data recorded in the activity log to calculate the total contact hours for each hospital in the intervention arm, as well as the number of contact hours spent on various activities. In each case we will summarise these data across all hospitals in the intervention arm using the median and interquartile range.

Efficacy Analysis

The effect of the intervention will be estimated through a cluster-level analysis. This approach is commonly used to analyse cluster-randomised trials and is considered preferable to an individual-level analysis when the number of clusters is small. It is usually recommended to use this approach to analyse cluster-randomised with fewer than 15 cluster per arm (Hayes and Moulton 2017).

Primary outcome

The cluster-level analysis approach will involve calculating the proportion of deaths among admissions separately for each hospital and then analysing these proportions via linear regression. Prior to inclusion in the regression model, the proportions will be logit-transformed [logit(p) = log(p/(1-p))] so that exponentiated regression coefficients can be interpreted as odds ratios.

To account for the matched design (control and intervention clusters were matched on baseline neonatal mortality), we will include baseline mortality as a linear term in the regression model. We chose this approach over including the matching variable itself (i.e., the variable indicating which matched triplet a particular cluster belongs to) for two reasons. First, including baseline mortality as a covariate uses fewer degrees of freedom (1 df versus 9 df), thereby increasing the statistical power of the analysis. Second, it allows us to use a more recent measure of baseline mortality, which is likely to be more closely correlated with outcome mortality. This, again, will increase statistical power.

A secondary analysis will adjust for case mix, i.e., differences between clusters in individual-level characteristics. This analysis will involve fitting an individual-level logistic regression model to the data. The model will include sex, birthweight, diagnosis at admission, age at admission, inborn-outborn status, month of admission and length of hospital stay as covariates, with the continuous variables (birthweight, age at admission and length of stay) modelled as cubic splines. The model will be used to predict the risk of neonatal mortality in each cluster based on case mix. We will then use linear regression to analyse the difference logit(observed proportion) – logit(predicted proportion). As with the primary analysis, the linear regression will include baseline mortality as a covariate.

In addition to conducting a formal statistical comparison, we will use boxplots to display the distribution of cluster proportions in the two study arms.

Secondary outcomes (clinical)

The secondary outcomes will be analysed using the same approach used for the primary outcome. The only difference will be that the baseline proportion of the outcome will be included in the model, in addition to baseline neonatal mortality. For outcomes where there are cluster proportions of 0%, we will add 1 observation to the numerator and denominator. Similarly, where cluster proportions are 100% we will subtract 1 from the numerator and denominator.

The format of the table of results is given in Table 2.

Secondary outcomes (management and experience of care)

Management and experience of care scores will be analysed using linear regression, adjusting for baseline scores and baseline neonatal mortality by including these variables as linear terms in the regression model. No adjustment will be made for case mix.

The data will not be logit-transformed; therefore, the regression coefficients will be interpreted as differences in means.

Missing Data

We will use an 'available case' approach to handle missing data, meaning that for each outcome, we will exclude individuals missing data on that outcome. For secondary outcomes assessed in a subgroup, such as the administration of antibiotics among neonates diagnosed with sepsis, individuals will be excluded if they are missing data on either the indicator (antibiotic use) or the subgroup (clinical diagnosis of sepsis).

Missing birthweight data

We note that a significant proportion of admissions (~7%) will be excluded from the analysis cohort because their birthweight is not recorded. We will explore the sensitivity of our findings to this missing data through a sensitivity analysis (see below).

Missing covariate data

In the analysis adjusted for case mix, we will again adopt an available case approach by fitting the logistic regression models to admissions with complete data on all covariates. We do not expect significant missing data in any of the covariates, except for birthweight, and missing data in this variable will be handled through the sensitivity analysis.

Missing data in management scores

The overall management score is computed by averaging scores across 26 component management practices. Where component scores are missing, the overall score will be computed by averaging across the non-missing component scores. A similar approach will be used for the score obtained from the review hospital management records.

However we note that because of the survey methodology (interviewers evaluating the responses of interviewees), it is unlikely that there will be any missing data in the management scores.

Sensitivity Analysis

Sensitivity analysis 1

The main analysis cohort excludes admissions where a birthweight is not recorded.

We will extend the analysis cohort by imputing missing birthweights from data on weight and age at admission.

The imputation will assume no growth on day 0/1 and a growth rate of 39g per day for males and 32g per day for females thereafter, based on WHO growth standards WHO Growth Standards.

Primary and secondary clinical outcomes will be analysed using this larger cohort.

Sensitivity analysis 2

To account for differences in the treatment effect across hospitals, we will analyse the primary and secondary clinical outcomes using weighted linear regression, with the weight being the number of hospital admissions (Kahan et al. 2023). Specifically, the weight used will be the number of admissions during the analysis period (1 April - 30 September, 2024). This approach produces a participant-average treatment effect (the average treatment effect across participants) rather than a cluster-average treatment effect (the average treatment effect across clusters).

Note that this approach will not be used as the primary analysis since weighted regression is often not efficient, i.e., it can lead to wide confidence intervals for the effect estimate (Leyrat et al., 2018).

Multiple Testing

No adjustment will be made for multiple testing.

Statistical Software

Analyses will be conducted using R version 4.4.0 and Stata version 18.0

References

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Dummy Tables and Figures

Figure 1: Consort diagram

Figure 2: Boxplots of primary and secondary outcomes by study arm

Table 1: Characteristics of neonatal admissions between 1 April 2024 and 30 Sep 2024 by study arm

	Intervention		Control	
	n/N	%	n/N	%
Sex				
Male				
Female				
Age at admissions (days)				
0				
1-3				
4-6				
7-28				
Age at admissions, Median, IQR				
Birth weight (g)				
<= 1000				
1001-1499				
1500-1999				
2000-2499				
2500-3999				
4000+				
Birth weight, Median, IQR				
Maternal Age (years)				
<20				
20-29				
30-39				
40+				
Maternal Age, Median, IQR				
Mode of delivery				
Vaginal				
Caesarean				

	Intervention		Control	
	n/N	**%**	**n/N**	**%**
Maternal HIV status				
Negative				
Positive				
Median baseline mortality per 100 admissions, IQR*				
Median number of monthly admissions, IQR				

*Baseline mortality will be assessed for the period 1 Jan 2023 – 30 June 2023

Table 2: Analysis of clinical outcomes

	Intervention		Control				
	n/N	**%**	**n/N**	**%**	**OR adj***	**95% CI**	**p-value**
Deaths (1ry outcome)							
Pulse oximetry done at admission							
Temperature taken at admission							
Glucose test done at admission							
All 3 diagnostics done at admission							
Breastfeeding at discharge							
Antibiotics given among clinical sepsis cases							
Absence of hypothermia							
KMC in newborns with low birthweight							

	Intervention		Control				
	n/N	**%**	**n/N**	**%**	**OR adj***	**95% CI**	**p-value**
Bilirubin test done for jaundice							
Phototherapy done for jaundice							
Blood culture done in newborns receiving antibiotics							
Blood culture done in clinical sepsis cases							
Receipt of CPAP among those in need							

*Odds Ratio adjusted for baseline mortality and baseline value of the outcome measure

Table 3: Analysis of management outcomes

	Intervention		Control				
	mean	**sd**	**mean**	**sd**	**Adj difference***	**95% CI**	**p-value**
Admissions per month							
Management score							
Record review score							

*Mean difference adjusted for baseline value of the outcome measure