Bedside Improvement of Resuscitation Through mHealth feedback (BIRTH Study)

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Protocol Version 3.0

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Protocol Signature Page

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I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with the provisions of this protocol, all requirements regarding the obligations of clinical investigators as fully outlined in the International Conference on Harmonization (Section E6(R2) Good Clinical Practice), local regulatory requirements, and the Investigator's Agreement, which I have also signed.

I have read and understand the information in the protocol and will ensure that all staff assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Investigator of Record Name: _____

Investigator of Record Signature: _____

Date: _____

Version Tracking

Version	Date	Comments
0.1	1/12/23	Submitted to UNC Scientific Review Committee (SRC)
1.0	5/9/23	Reflects changes recommended by UNC SRC; submitted to UNC SRC for subsequent review; also removal of audio-video recording
2.0	1/18/24	Reduction of study sites from six health facilities to four
3.0	2/13/24	Change of primary outcome

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ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIM	Acceptability of Intervention Measure
BIRTH	Bedside Improvement of Resuscitation Through mHealth feedback
BMV	bag mask ventilation
bpm	beats per minute
Co-I	Co-investigator
DRC	Democratic Republic of the Congo
FIM	Feasibility of Intervention Measure
HBB	Helping Babies Breathe
HR	heart rate
IRB	institutional review board
KSPH	Kinshasa School of Public Health
LDHF	low-dose, high-frequency
LMICs	low- and lower middle-income countries
mHealth	mobile health
NICHD	National Institute of Child Health and Human Development
DASH	Data and Specimen Hub
PI	Principal Investigator
RTI	Research Triangle Institute International
s	seconds (e.g., 30s is 30 seconds)
SAE	serious adverse event
SUS	System Usability Scale
UNC	University of North Carolina

STUDY SUMMARY

Title	Bedside Improvement of Resuscitation Through mHealth feedback
Short Title	BIRTH Study
Methodology	Pre-post trial with cluster randomization to one of two interventions
Purpose	To evaluate the effectiveness of newborn resuscitation feedback supported by a mobile health application called LIVEBORN; secondarily, to evaluate the relative effectiveness of real-time guidance vs debriefing
Study Participants	Newborns and nurse midwives
Study Activities	*Pilot phase:* Establishment of systems for implementation of recommended training and simulation practice and consistent use of LIVEBORN for observing resuscitations. *Control phase:* Implementation of recommended basic resuscitation training and low-dose, high-frequency practice of bag mask ventilation. *Intervention phase:* Implementation of either LIVEBORN real-time guidance or debriefing in addition to recommended practice.
Study Sites	Four health facilities in Kinshasa, Democratic Republic of the Congo
Eligibility Criteria	Newborns admitted to a participating health facility who meet the following criteria— *Inclusion criteria:* All in-born neonates, either liveborn or intrapartum (i.e., fresh) stillborn, regardless of multiple gestation or maternal complication. *Exclusion criteria:* Less than 28 weeks completed gestation (or if gestational age is unknown, birth weight <1,000 grams), outborn, known congenital anomaly, or antepartum (i.e., macerated) stillbirth. Nurse midwives employed at a participating health facility who meet the following criteria— *Inclusion criteria:* All midwives and nurses functioning in the role of a midwife who care for newborns at the time of birth during the course of their regular employment. *Exclusion criteria:* Unwillingness to consent.

Outcomes

Primary Outcome:

Total duration of suctioning among all newborns

Secondary Outcomes:

Duration of suctioning among newborns who do not cry by 30s
Duration of suctioning among newborns who cry by 30s
Suctioned for <30s among newborns who do not cry by 30s
Suctioned among newborns who cry by 30s
Time to bag mask ventilation
Bag mask ventilation within 60s after birth
Receipt of bag mask ventilation
Time to heart rate ≥ 100 bpm
Time to first cry
24-hour newborn mortality
Perinatal mortality
Stillborn misclassification

1 INTRODUCTION

This document is a protocol for a human research study. The Bedside Improvement of Resuscitation Through mHealth feedback (BIRTH) study is to be conducted according to applicable government regulations, and institutional research policies and procedures.

1.1 STATEMENT OF THE PROBLEM

Almost one million newborns die each year from failure to breathe at birth. Nearly all of these deaths occur in low and lower-middle income countries (LMICs). Timely and continuous bag mask ventilation (BMV) reduces these deaths. However, BMV is often delayed and interrupted, limiting its potential to save lives. In particular, frequent and prolonged suctioning contributes to delayed and interrupted BMV. There is strong scientific premise for improving resuscitation care at the bedside using feedback strategies such as real-time guidance and debriefing. Mobile health (mHealth) technology could enable implementation of feedback strategies in LMICs.

1.2 BACKGROUND AND RATIONALE

Respiratory depression causes most newborn deaths in the first 24 hours after birth. One million newborns die on their day of birth each year, accounting for one third of all newborn deaths.[1] Ninety percent of these deaths are from failure to breathe at birth (i.e., respiratory depression).[2] Nearly all of these deaths occur in LMICs.

Timely and continuous BMV reduces newborn mortality from respiratory depression. Basic resuscitation practices reduce death from respiratory depression. Among these practices, BMV has the greatest impact on mortality. To be effective, BMV must be timely. Resuscitation algorithms recommend initiating BMV of non-breathing newborns within 60 seconds (s) after birth.[3,4] Delayed BMV increases the risk of death: for every 30s delay in BMV, the risk of death or hospitalization increased by 16% in a hospital in Tanzania.[5,6] Effective BMV is also continuous. Resuscitation algorithms recommend continuous ventilation until spontaneous breathing begins. Interrupted BMV increased the risk of death by 75% in the same hospital in Tanzania.[7]

Simulation-based training is the recommended strategy for implementation of basic resuscitation, but is insufficient to ensure quality care. The recommendation to implement basic resuscitation practices is simulation training using a resuscitation algorithm such as Helping Babies Breathe (HBB).[8] HBB is an educational program developed by the American Academy of Pediatrics that teaches basic resuscitation skills for providers in low-resource settings using simulation. HBB training reduces perinatal mortality. However, sustaining this reduction is challenging due to a decline in resuscitation knowledge and skill over time following training.[8,9] Low-dose, high-frequency (LDHF) simulation practice of BMV (for example, practicing BMV on a manikin for a few minutes at the start of each shift) reduces this decline, and has become part of recommended practice for implementation of basic resuscitation in low-resource settings. However, despite HBB with LDHF practice, gaps in quality care at the bedside remain.

Improving BMV is critical to reduce newborn death in LMICs such as the Democratic Republic of the Congo (DRC). In 2018, the newborn mortality rate in the DRC was 28.3 per 1,000 live births.[10] Since 2005, the newborn mortality rate in the DRC has declined by an average of only 0.6 deaths per 1,000 live births per year. At this pace of mortality reduction, the DRC will not meet the 2030 Sustainable Development Goal of 12 per 1,000 live births until after 2050.[11,12] In response, the DRC Ministry of Health and USAID began a seven year plan to implement HBB training with frequent simulation practice

in 178 health zones starting in 2019.[13] This training is likely to reduce mortality. However, reductions will be limited unless complementary, scalable strategies are developed to ensure effective BMV.

Suctioning contributes to delayed and interrupted BMV. Resuscitation studies in LMICs indicate that BMV is delayed in up to 78% of resuscitations, with a mean initiation time of as long as 220s after birth.[14,15] BMV is also intermittent rather than continuous in 50% of these resuscitations.[16] In our clinical trial in the DRC, frequent and prolonged suctioning contributed to delayed and interrupted BMV.[17] Initiation of BMV was delayed with a median initiation time of 326s after birth; suctioning contributed to this delay. BMV was also frequently interrupted, with pauses lasting a median of 22s; suctioning was commonly performed during these pauses. Over the course of a resuscitation, providers spent a median of 68s suctioning babies who were not breathing well, and 98s suctioning newborns who received BMV. Among newborns who received BMV, the average duration of one suctioning episode was 30s. In addition to contributing to delayed and interrupted BMV, suctioning can have harmful side effects such as vagal-induced bradycardia,[18] increased risk of infection,[19,20] lower oxygen saturation,[20-23] apnea,[24] and neonatal brain injury.[25,26]

There is strong scientific premise for improving resuscitation with feedback strategies. Feedback on cardiopulmonary resuscitation for health professionals improves their performance.[27-36] Two feedback strategies for improving resuscitation during simulation have demonstrated effectiveness: *real-time guidance* (feedback during practice) and *debriefing* (feedback after practice).[37-44] In high-income countries, these strategies are typically implemented using expert clinicians and detailed data on resuscitation events. Feedback in LMICs is likely to have similar and significant impact. However, lack of both expert clinicians and detailed data are significant barriers to bedside feedback in LMICs. mHealth technology could enable the implementation and evaluation of these strategies in LMICs.

We will evaluate the impact of bedside feedback on resuscitation care and neonatal outcomes using an mHealth app called LIVEBORN. In the R21 phase of this work, we developed LIVEBORN, an mHealth app that provides feedback on clinical performance of newborn resuscitation. Using the LIVEBORN app, an observer documents the timing of key actions of the provider and the respiratory status of the newborn (Figure 1). LIVEBORN communicates via Bluetooth with a battery-operated heart rate (HR) meter called NeoBeat to

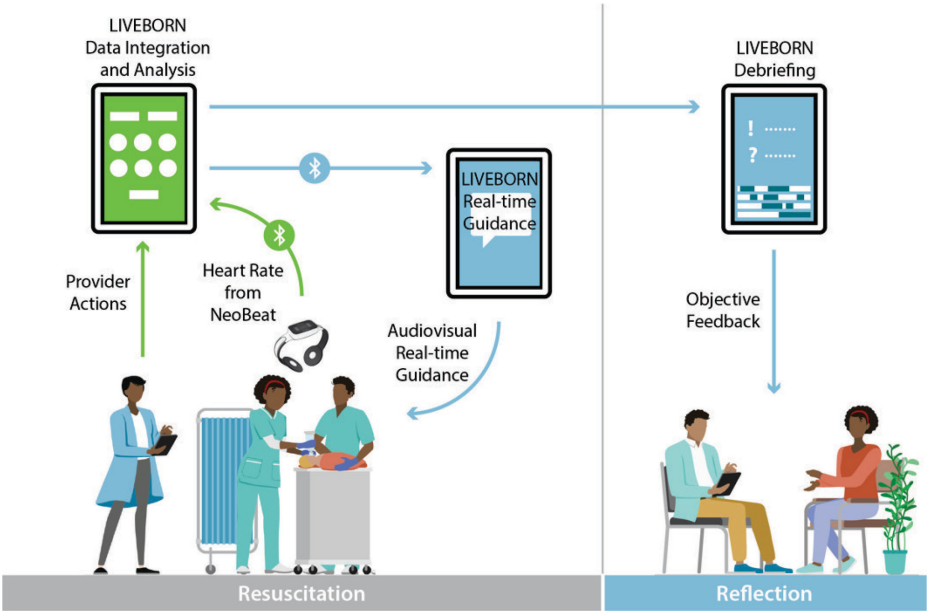


Figure 1. LIVEBORN incorporates data on resuscitation care from an observer and heart rate data from a battery-operated heart rate meter called NeoBeat to identify depressed newborns and provide automated feedback. Using trials of improved practices, we developed an integrated strategy to incorporate LIVEBORN into clinical practice that included the following elements: 1) who observes births with LIVEBORN, 2) which births are observed, 3) a system for cleaning and charging NeoBeat, 4) a system for charging and storing the LIVEBORN tablet, 5) a system for preparing all resuscitation equipment including NeoBeat and the tablet, and 6) a plan for communicating the strategy. At the facility implementing debriefing, the strategy also included: 1) who debriefs, 2) what cases are debriefed, and 3) when debriefing occurs.

record the HR of the newborn throughout the resuscitation (Figure 2). NeoBeat uses dry electrode technology to digitally display HR, is easily placed by a single provider, and was previously evaluated in our clinical trial in the Democratic Republic of the Congo (DRC).[45] In this trial, midwives perceived that HR monitoring enabled their resuscitation care, and desired to continue using the device beyond the trial.[46] The LIVEBORN app integrates data from the observer and NeoBeat to provide audio-visual real-time guidance during a resuscitation and to support debriefing after a resuscitation.

Figure 2. NeoBeat is a low-cost device for the measurement of newborn heart rate (HR) that was developed by Laerdal Global Health for use in low-resource settings. It is applied by placing the device around the torso of the newborn. It detects HR accurately, quickly (<5 sec), is reusable and can be easily disinfected. NeoBeat's dry electrodes detect HR which is both displayed on a bright LED-display and recorded. A single birth attendant can apply NeoBeat in 2-3 seconds and use it to identify a HR after birth in a non-breathing newbornto guide further management, including bag-mask ventilation.

Image from: Laerdal Global Health. https://shop.laerdalglobalhealth.com/product/neobeat/

We have demonstrated that LIVEBORN can be successfully incorporated into clinical care in health facilities in the DRC. In the R21 phase of this work, we developed an integrated 6-element strategy for incorporating LIVEBORN into clinical care in an iterative process with midwives (Figure 1). The strategy included selection of observers for LIVEBORN and which births to observe. Midwives implemented the final strategy in a feasibility study, and found LIVEBORN both usable and feasible to incorporate into their clinical practice (data not published).[47] This prior work supports our evaluation of LIVEBORN in this clinical trial.

2 Study Objective, Specific Aim and Outcomes

2.1 Study Objective

Our objective is to reduce newborn mortality by improving resuscitation care in LMICs through bedside feedback using an innovative mHealth app called LIVEBORN.

2.2 Specific Aim

We aim to evaluate the effectiveness of LIVEBORN feedback in a clinical trial with randomization to real-time guidance or debriefing.

2.3 Primary Outcome

Our primary outcome is the total duration of suctioning among all newborns.

2.4 Secondary Outcomes

Our secondary outcomes are as follows:

- Duration of suctioning among newborns who do not cry by 30s

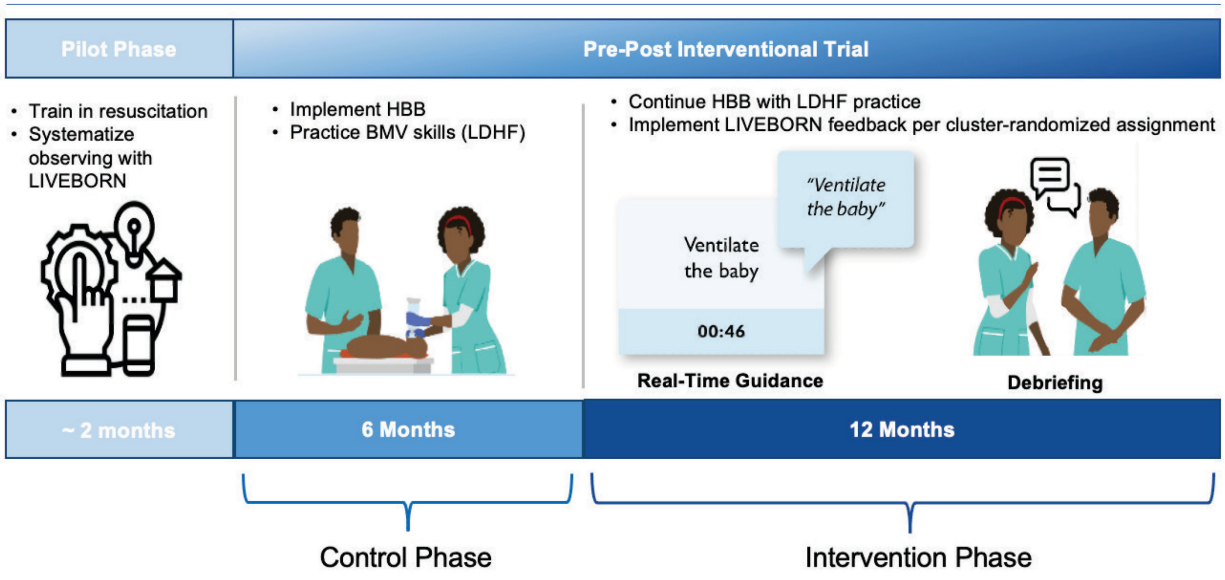
- Duration of suctioning among newborns who cry by 30s
- Suctioned for <30s among newborns who do not cry by 30s
- Suctioned among newborns who cry by 30s
- Time to BMV
- BMV within the Golden Minute
- Receipt of BMV
- Time to HR ≥ 100 bpm
- Time to first cry
- 24-hour newborn mortality
- Perinatal mortality
- Stillborn misclassification

3 METHODOLOGY

3.1 STUDY DESIGN

This is a pre-post interventional trial to evaluate the effectiveness of LIVEBORN feedback. We will use a randomized design to test the relative effectiveness of two modes of feedback: real-time guidance versus debriefing. Given the potential for feedback interventions to have spillover effects, we will randomize by cluster (i.e., facility) rather than by individual. The study will begin with an approximately two-month pilot phase to establish systems for implementation of recommended training and simulation practice and consistent use of LIVEBORN for observations (Figure 1). After these systems have been successfully established, we will initiate the pre-post trial. The control phase will last six months followed by implementation of LIVEBORN feedback in an intervention phase lasting 12 months.

Figure 3. Study Design



3.2 STUDY SITES

We will conduct this pre-post interventional trial in four health facilities in Kinshasa, DRC. Given typical staffing and annual birth rates at participant facilities, we anticipate enrolling up to 25,000 newborns and 150 nurse midwives.

3.3 STUDY POPULATION

The population for this study will consist of newborns and nurse midwives. The intervention will be directed towards nurse midwives.

3.3.1 Newborns

Newborns admitted to a participating health facility who meet the following criteria:

Inclusion criteria:
All in-born neonates, either liveborn or intrapartum (i.e., fresh) stillborn, regardless of multiple gestation or maternal complication.

Exclusion criteria:
Less than 28 weeks completed gestation (or if gestational age is unknown, birth weight <1,000g), outborn, known congenital anomaly, or antepartum (i.e., macerated) stillbirth.

3.3.2 Nurse Midwives

Nurse midwives employed at a participating health facility who meet the following criteria:

Inclusion criteria:
All midwives and nurses functioning in the role of a midwife who care for newborns at the time of birth during the course of their regular employment.

Exclusion criteria:
Unwillingness to consent.

4 STUDY PROCEDURES

The following section describes study participant activities and data collection as summarized in Table 1.

Table 1. Schedule of study procedures

	Pilot	Control	Intervention
Study Participant Activities			
Nurse midwife informed consent & enrollment	x	x	x
HBB training with NeoBeat	x		
LIVEBORN observer training	x		
Weekly LDHF practice of BMV	x	x	x
Observe births with LIVEBORN	x	x	x
Place NeoBeat on non-breathing newborns	x	x	x
Orientation to LIVEBORN feedback		x†	
Debriefing training (debriefing facilities only)		x†	
LIVEBORN real-time guidance OR debriefing§			x
Data Collection Activities			
Nurse midwife demographics (BIRTH-01)	x	x	x

Small-scale testing: direct observations and semi-structured interviews (BIRTH-02)	x		
Resuscitation knowledge and skills	x		
Simulation practice of BMV (NeoNatalie Live app)	x	x	x
Key resuscitative actions (LIVEBORN app)	x	x	x
Newborn respiratory status (LIVEBORN app)	x	x	x
Newborn electrocardiographic tracing (NeoBeat)	x	x	x
Medical record abstraction		x	x
Facility culture and energy for work (BIRTH-08)			x
Checklist for debriefing facilitator §			x
Feasibility and acceptability of LIVEBORN (BIRTH-03)			x

† at end of control

§ per cluster randomization

4.1 PARTICIPANT RECRUITMENT

Prior to study activation, we will seek the necessary facility-level approvals from facility leadership. We will approach all nurse midwives employed at participating facilities for informed consent to enroll at the start of the trial; if new nurse midwives are employed during the study period, we will also approach them for informed consent to enroll.

4.2 PARTICIPANT SCREENING AND ENROLLMENT

4.2.1 Newborns

All eligible neonates will be enrolled in the study under a waiver of informed consent. These newborns' participation in the study is limited to data collection only, including 1) medical record abstraction and 2) for a convenience sample, collection of data relevant to the newborn's condition at and around birth with LIVEBORN and NeoBeat. This waiver of informed consent is justified as the research involves no greater than minimal risk to newborns or to their privacy, the waiver will not adversely affect the rights and welfare of newborns, the research would be impracticable to conduct without the waiver, and the risk to privacy is reasonable in relation to the importance of the knowledge to be gained.

Research staff will assess basic eligibility criteria using the health facility delivery register prior to enrolling the neonate in the study. Some eligibility criteria may not be determinable prior to birth. For example, if gestational age is unknown, birth weight can only be ascertained after birth. Additionally, some congenital anomalies may be readily noticeable at birth (such as an abdominal wall defect), but unknown prior to birth due to lack of prenatal ultrasound as standard of care in the DRC. Since collection of resuscitation data in this study depends upon real-time data collection at birth, we will collect resuscitation data at the time of birth on a convenience sample of all potentially eligible participants using the LIVEBORN app and NeoBeat. If, following birth and observational data collection, it is determined that the newborn does not meet eligibility criteria, the data will be deleted.

4.2.2 Nurse Midwives

Using a list of all providers working at each facility obtained from facility leadership, research staff will reach out to potential participants. Research staff will assess basic eligibility criteria. Details of the informed consent process are included in Section 7 of this protocol. At the time of enrollment, each nurse midwife will complete a demographic survey (BIRTH-01 Nurse Midwife Demographics).

4.3 PILOT PHASE

The purpose of the pilot phase is to establish systems to ensure 1) implementation of recommended training and simulation practice and 2) consistent use of LIVEBORN for observations.

Our specific aim is to develop a contextually-appropriate strategy for each facility that results in implementation of LIVEBORN observations for at least 50% of births.

The pilot phase will last approximately two months. Any facilities deemed facile with LIVEBORN will be exempted from the pilot phase.

4.3.1 Establishment of a System for Implementation of Recommended Training and Simulation Practice

During the pilot phase, we will work with each facility to ensure a system for implementation of recommended resuscitation training and LDHF practice of BMV.

4.3.1.1 Basic Resuscitation Training

We will train all nurse midwives in basic resuscitation using HBB 2.0 materials adapted to include NeoBeat. In addition to reviewing the evidence-based HBB resuscitation algorithm, research staff will orient nurse midwives to use of NeoBeat, including how to place the device, interpretation of its digital display and standard processes for cleaning and charging the device. The training will also include how to use HR to accurately distinguish liveborn from stillborn infants. We will recommend that nurse midwives use NeoBeat for high-risk pregnancies and newborns not crying by 30s.

4.3.1.2 LDHF Practice of BMV

We will work with the head nurse midwife at each participating health facility to establish a system for nurse midwives to regularly practice their BMV skills using a manikin such as NeoNatalie Live. We will recommend a goal of once weekly practice. The KSPH Study Coordinator and KSPH Study Physician will monitor adherence to regular practice during the trial, and work with the head nurse midwife to improve adherence as necessary.

4.3.2 Establishment of a System for Consistent Use of LIVEBORN for Observations

During the pilot phase, we will work with each facility to ensure a system for consistent use of LIVEBORN for observations. This system will include placement of NeoBeat on newborns requiring resuscitation.

4.3.2.1 Training in Observing Births with LIVEBORN

We will orient all nurse midwives to the LIVEBORN app in training sessions. Training will include a guided tour of LIVEBORN and practice with event registration. Research staff will determine when each nurse midwife has demonstrated sufficient accuracy to begin observing resuscitations on the labor and delivery ward.

If individuals other than nurse midwives are identified as potential bedside observers during strategy development (see section 4.3.2.2), we will also train these individuals to conduct LIVEBORN observations in similar manner to the process described above. We will maintain a current log of individuals trained to observe resuscitations with LIVEBORN at each facility.

4.3.2.2 Strategy Development for LIVEBORN Observation

We will use an established participatory research methodology called trials of improved practices (TIPS) which we successfully used in the R21 phase of this work to design a strategy for consistent use of

LIVEBORN for observations. TIPS engages stakeholders in the design of behavior change activities through an iterative process involving strategy development, small-scale testing and rapid analysis.[48] TIPS allows participants to try a strategy in the clinical environment for a period of time and then provide feedback about its acceptability and feasibility for their context. Findings generated by this approach help researchers identify potential barriers, develop strategies to overcome those barriers, and eliminate or modify intervention components that are not feasible for participants.

At each facility, we will conduct a strategy development session with facility leadership such as the head nurse midwife to develop an initial strategy for LIVEBORN that includes selection of the following elements:

- Identification of bedside observers who will register resuscitation events in the LIVEBORN app such as labor and delivery leadership, providers themselves, trainees or other ancillary staff (Of note, research staff will also be available to conduct observations approximately 40 hours per week; providers will only serve as observers if they are not providing care at the time of the resuscitation)
- System for use of NeoBeat, including preparation prior to birth, cleaning and charging
- System for use of the LIVEBORN tablet, including preparation prior to birth, charging and storing

Each health facility will implement the locally-developed initial strategy in a small-scale test for approximately three weeks. Throughout the small-scale test, we will rapidly analyze data and identify barriers to implementation of the strategy as well as potential solutions. While the target length for the small-scale test will be three weeks, each small-scale test may be shorter or longer depending on when the strategy has been consistently implemented for a long enough period to determine what is working well and what could be improved. We will determine the ultimate length of each small-scale test based on on-going analysis of the data and in conjunction with the head nurse midwife. We will refine the strategy in additional cycles of TIPS (strategy development, small-scale testing, rapid analysis) until we have identified a feasible strategy to move into the control phase.

4.3.3 Data Collection

The following section describes the data we will collect during each aspect of the pilot phase, as summarized in Table 1.

4.3.3.1 Basic Resuscitation Training

We will evaluate nurse midwives' knowledge and skills before and after training using standard course materials adapted to include NeoBeat. For each resuscitation training, research staff will record nurse midwife attendance and the results of all knowledge and skills evaluations for each nurse midwife including such items as a knowledge questionnaire, a BMV skills check, and objective structure clinical exams. If a nurse midwife does not pass any of the knowledge and skills evaluations, we will conduct additional training to improve scores to a passing rate.

4.3.3.2 LDHF Practice of BMV

We will collect data on the frequency of practice sessions for each provider. If practicing with NeoNatalie Live, we will also collect data on the quality of practice sessions including ventilation rate and pressure using the accompanying NeoNatalie Live app.

4.3.3.3 Strategy Development for LIVEBORN Observations

During TIPS, research staff will document the details of the agreed-upon strategy for each round. During small-scale testing, research staff will gather data on each element of the strategy through direct observations, including who is observing births with LIVEBORN, how NeoBeat is being cleaned and charged and how the tablet is being charged and stored. Additionally, the Study Coordinator or Study Physician will conduct a convenience sample of semi-structured interviews of nurse midwives to evaluate acceptability and feasibility (BIRTH-02 Semi-structured interview guide).

Trained observers (research staff, nurse midwives, and other designated observers per the strategy developed in 4.3.2) will conduct observations of resuscitations for a convenience sample of births using the LIVEBORN app. If NeoBeat is placed on the newborn, we will collect HR and electrocardiographic (ECG) data.

4.3.4 Criteria for Transition to the Control Phase

Given our prior work with TIPS, we anticipate quickly arriving at feasible strategies in these four new facilities and thus estimate a need for two to three TIPS cycles per facility. Our target goal to move into the control phase will be a strategy that facilitates the observation of 65% of births. However, we will consider advancing facilities to the control phase despite a lower rate of observations if the overall sample size for observations in the pilot at all four facilities combined is adequate to maintain power for the clinical trial. As facilities may reach the target goal after varying amounts of time in the pilot phase, the start date of the control phase may vary per facility.

4.4 CONTROL PHASE

The purpose of the control phase is to gather detailed, prospective data on resuscitation care and newborn outcomes while implementing recommended practice.

4.4.1 Implementation of Helping Babies Breathe with Low-Dose, High-Frequency Practice

During a six-month control phase, midwives will implement HBB in their clinical practice with LDHF simulation practice of BMV. LDHF practice will occur at regular intervals per the system set up during the pilot phase. Nurse midwives will place NeoBeat on newborns that they anticipate resuscitating.

4.4.2 Data Collection

Research staff will conduct medical record abstraction to document clinical data for each eligible newborn including such elements as maternal parity and age, birth date and time, infant gestational age, birth weight, mode of delivery, stillborn or liveborn, alive or dead at discharge (including date of death).

As in the pilot phase, trained observers (research staff, midwives, and other designated observers per the strategy developed in the pilot phase) will conduct observations of resuscitations for a convenience sample of births using the LIVEBORN app. If NeoBeat is placed on the newborn, we will collect ECG data.

4.4.3 Preparatory Activities for the Intervention Phase

While in the control phase, we will randomize facilities to either real-time guidance or debriefing with LIVEBORN in preparation for the intervention phase (see section 6.2). Prior to implementation of the intervention and towards the end of the control phase, research staff will prepare nurse midwives to implement LIVEBORN feedback per their cluster randomized assignment using simulation.

4.4.3.1 Preparation for Debriefing

For facilities randomized to debriefing, research staff will work with the head nurse midwife to develop a strategy for debriefing that includes who will debrief, for what cases, and when debriefing will occur. Research staff will also conduct a half-day training with nurse midwives in debriefing using a curriculum we have developed for this purpose. Debriefing training will cover the goal of debriefing, review how to debrief, and discuss how to create a safe and supportive environment for debriefing. The training will include the presentation of positive and negative examples of debriefing, and incorporate simulation practice of debriefing with several cases embedded in the LIVEBORN app.

4.4.3.2 Preparation for Real-Time Guidance

For facilities randomized to real-time guidance, research staff will orient providers to LIVEBORN real-time guidance with such activities as demonstration and simulation practice. Staff will also discuss how to create a safe and supportive environment for real-time guidance.

4.5 INTERVENTION PHASE

The purpose of the intervention phase is to gather prospective data on resuscitation care and newborn outcomes during implementation of LIVEBORN feedback. During this 12-month phase, nurse midwives will implement LIVEBORN feedback per their cluster-randomized assignment to either real-time guidance or debriefing. Additionally, nurse midwives will continue all study procedures from the control phase, including implementation of HBB with LDHF practice, use of NeoBeat on newborns requiring resuscitation, and observation of births using LIVEBORN.

4.5.1 Implementation of LIVEBORN Feedback

At facilities randomized to real-time guidance, midwives will be supported by audio-visual feedback from LIVEBORN during the convenience sample of resuscitations observed with LIVEBORN. At facilities randomized to debriefing, midwives will debrief with LIVEBORN for at least 50% of the convenience sample of resuscitations observed with LIVEBORN that involved a newborn not crying by 60 seconds after birth and/or the receipt of BMV.

4.5.2 Basic Resuscitation Training

There is no literature to support a particular interval for frequency of HBB training. The Neonatal Resuscitation Program requires training every two years to maintain certification, thus we will target a training frequency that is at least every two years for HBB during this trial. After all facilities have initiated the control phase, and depending on the length of the pilot phase, we will determine whether repeat HBB training should be conducted during the intervention and standardize this across the sites. If HBB training is conducted during the intervention phase, we will follow the procedures described in section 4.3.1.1.

4.5.3 Data Collection

As in the control phase, research staff will conduct medical record abstraction to document clinical data for each enrolled newborn including such elements as maternal parity and age, birth date and time, infant gestational age, birth weight, mode of delivery, stillborn or liveborn, alive or dead at discharge (including date of death).

As in the pilot and control phases, trained observers (research staff, midwives, and other designated observers per the strategy developed in the pilot phase) will conduct observations of resuscitations for a

convenience sample of births using the LIVEBORN app. If NeoBeat is placed on the newborn, we will collect ECG data.

At the start of the intervention, approximately six months into the intervention phase, and again at the end of the intervention, midwives at all facilities will complete a survey on their facility culture and energy for work (Facility Culture and Energy for Work; BIRTH-08). In the debriefing facilities, trained observers will also observe a convenience sample of debriefing sessions and coach facilitators on improving their debriefing sessions.

At the end of the intervention, five midwives & the head nurse midwife from each facility will complete surveys consisting of 4-item quantitative scales to evaluate feasibility and acceptability (Feasibility of Intervention Measure [FIM] and Acceptability of Intervention Measure [AIM]; BIRTH-03).[49]

5 DEFINITION OF OUTCOMES

5.1 PRIMARY OUTCOME

5.1.1 Duration of Suctioning Among All Newborns

Although not recommended by HBB, suctioning is frequently used among crying babies; when used excessively in non-crying babies, it also contributes to delayed BMV. LIVEBORN feedback will provide guidance to limit suctioning. We will measure duration of suctioning as a continuous variable and report summary statistics including mean, standard deviation, median, and quartiles for total seconds spent suctioning all newborns between birth and 10 minutes after birth (or when LIVEBORN observation ceases, whichever is sooner). We will compare this outcome between the control and intervention groups. If LIVEBORN feedback is effective based on this outcome, we will compare duration of suctioning between real-time guidance and debriefing groups.

5.2 SECONDARY OUTCOMES

We will compare the following secondary outcomes reflecting resuscitation care and neonatal outcomes between the control and intervention groups. If LIVEBORN feedback is effective based on a given secondary outcome, we will compare the same outcome between real-time guidance and debriefing groups.

5.2.1 Duration of Suctioning Among Newborns Who Do Not Cry By 30s

HBB recommends suctioning to clear the airway as needed for newborns who do not cry, followed by BMV for newborns who are not breathing well. In our clinical trial of NeoBeat, providers engaged in excessive suctioning of non-crying newborns resulting in delays in initiating BMV. We will measure duration of suctioning as a continuous variable and report summary statistics including mean, standard deviation, median, and quartiles for total seconds spent suctioning newborns who do not cry by 30s after birth between birth and 10 minutes after birth (or when LIVEBORN observation ceases, whichever is sooner).

5.2.2 Duration of Suctioning Among Newborns Who Cry By 30s

In our clinical trial of NeoBeat, providers engaged in excessive suctioning of newborns who were breathing well by 30s after birth. We will look at our primary outcome of duration of suctioning in the subset of all livebirths who cry by 30s after birth. We will measure duration of suctioning as a continuous variable and report summary statistics including mean, standard deviation, median, and quartiles for total seconds spent suctioning newborns who cry by 30s after birth between birth and 10 minutes after birth (or when LIVEBORN observation ceases, whichever is sooner).

5.2.3 Suctioned For <30 Seconds Among Newborns Not Crying By 30s

Although HBB does not recommend a particular range for the amount of time spent suctioning, it does emphasize the potential harmful effects of excessive suctioning. We will use a conservative benchmark of less than 30s as a reasonable timeframe for suctioning. We will look at a dichotomous variable related to suctioning among newborns who do not cry by 30s after birth. We will report the proportion of livebirths not crying by 30s who are suctioned for less than 30s between birth and 10 minutes after birth (or when LIVEBORN observation ceases, whichever is sooner).

5.2.4 Suctioned Among Newborns Who Cry By 30s

HBB does not recommend suctioning for crying babies. Since LIVEBORN feedback will provide guidance on limiting suctioning of well babies, we will also look at a dichotomous variable related to suctioning among newborns who cry by 30s after birth. We will report the proportion of livebirths crying by 30s who are suctioned between birth and 10 minutes after birth (or when LIVEBORN observation ceases, whichever is sooner).

5.2.5 Time to Bag Mask Ventilation

HBB recommends initiation of BMV within 60s after birth, and delayed BMV has been significantly linked to increased mortality. We will measure time to BMV as a continuous variable, defining time to BMV as the number of seconds between birth and the start of BMV. We will report summary statistics including mean, standard deviation, median, and quartiles for time to BMV among all livebirths not crying by 30s who receive BMV.

5.2.6 Bag Mask Ventilation within 60s After Birth

In addition to time to BMV, we will measure a dichotomous variable of BMV initiation within 60s after birth. We will report the proportion of newborns who receive BMV within the golden minute among all livebirths not crying by 30s who receive BMV.

5.2.7 Receipt of Bag Mask Ventilation

HBB recommends initiation of BMV for all newborns who are not breathing by 60s after birth. In a prior clinical trial in the DRC, we demonstrated that BMV is underused with only 19.7% of newborns not breathing by 60s receiving BMV. Due to the subjectivity of observed breathing status, we will use the more objective metric of crying by 60s. We will measure a dichotomous variable of receipt of BMV at any point during delivery room resuscitation and report the proportion of livebirths not crying by 60s who receive BMV.

5.2.8 Time to Heart Rate ≥100 Beats Per Minute

HR is a sensitive indicator of the adequacy of spontaneous respirations and the response to resuscitative interventions. We will measure the time to HR≥100bpm as a continuous variable. Among livebirths who

have not cried by 30s after birth who have NeoBeat placed, we will report summary statistics including mean, standard deviation, median, and quartiles for time from birth until first HR ≥100bpm.

5.2.9 Time to First Cry

Crying generally indicates that HR ≥100bpm. Since we anticipate that NeoBeat will not be used in all newborns who have not cried by 30s, we will also measure time to first cry as a continuous variable. We will report summary statistics including mean, standard deviation, median, and quartiles for time to first cry among livebirths who have not cried by 30s.

5.2.10 24-hour Newborn Mortality

In the participating health facilities, typical length of stay following birth is more than 24 hours. In the rare instance when a newborn is discharged home prior to 24 hours after birth, we will assume the newborn is alive at 24 hours. If the newborn is transferred prior to discharge, we will contact the referral facility to determine 24-hour vital status. We will measure 24-hour newborn mortality as a dichotomous variable for all enrolled newborns, and report the proportion of livebirths who have died by 24 hours after birth.

5.2.11 Perinatal Mortality

We hypothesize that LIVEBORN feedback will prompt resuscitation in cases previously presumed futile and classified as stillborn. While accurately classifying and resuscitating these liveborn cases could increase the overall risk of mortality, it should not result in increased perinatal mortality. We will define perinatal mortality as fresh stillbirths plus neonatal mortality in the first 24 hours. We will define fresh stillbirths based on the provider's documentation in the medical record. We will measure perinatal mortality as a dichotomous variable for all enrolled newborns, and report the proportion of births resulting in a fresh stillbirth or neonatal death in the first 24 hours.

5.2.12 Stillbirth Misclassification

Stillbirth misclassification in low-resource settings, particularly the misclassification of a neonatal death as a fresh stillbirth, has been previously reported in the literature.[50,51] Basic resuscitation training reduces fresh stillbirths via a reduction in this misclassification.[52-57] In our prior clinical trial of basic resuscitation augmented with continuous electronic HR monitoring in the DRC, total stillbirth rates did not change with the intervention. However, we demonstrated a misclassification rate of 20% during the intervention period compared to a misclassification rate of 44-58% reported in prior literature,[55,58,59] suggesting that electronic HR monitoring further reduced misclassification beyond basic resuscitation training alone.[45]

LIVEBORN feedback is designed to instruct providers to attempt resuscitation of all liveborn and fresh stillborn infants, in keeping with Helping Babies Breathe recommendations. The feedback does not address whether the provider's diagnosis of stillbirth is accurate or not. However, we hypothesize that LIVEBORN feedback may reduce misclassification compared to basic resuscitation training with HR monitoring alone by encouraging providers to initiate resuscitation of newborns they presume are freshly stillborn. These neonates may demonstrate signs of life during resuscitation that will prompt the provider to accurately classify them as liveborn even in the event of death in the delivery room.

In this study, we will not eliminate bias in stillbirth misclassification. To do so would require consistent use of both fetal heart rate monitoring and neonatal heart rate monitoring, neither of which are standard of care in the study facilities. However, we will review the subset of stillbirth cases with HR

data from NeoBeat to determine whether the case is stillborn or liveborn based on HR. We will define misclassification as cases identified by a provider as stillborn who have a HR per NeoBeat. We will measure the dichotomous outcome of stillbirth misclassification and report the proportion of stillbirths that are misclassified.

6 DATA MANAGEMENT AND ANALYSIS

6.1 DATA SECURITY AND MANAGEMENT

Study data management will follow procedures outlined in the manual of operations. Participant identification numbers will be used on all forms and communications related to the study. A separate, confidential participant log will link study identification numbers and participants' names. All data instruments and logs will be securely stored. All study computers and tablets will be password protected and their access restricted to authorized study personnel. Data will be transmitted electronically to the study investigators through secure, cloud-based servers.

Table 2 describes how data collection will be accomplished. Any data collected using paper instruments will be entered into a database such as KoboCollect by research staff. Data from the NeoNatalie Live app, LIVEBORN app and NeoBeat apps will be uploaded to a password-protected cloud-based server. As the health facilities do not have internet access, data will be stored on password-protected tablets with approximately weekly interval upload to secure, cloud-based servers when internet is available.

Table 2. Data collection methods

Data collection	Method
Nurse midwife demographics (BIRTH-01)	Paper survey or tablet-based entry, based on convenience
Small-scale testing: direct observations and semi-structured interviews (BIRTH-02)	Paper instruments
Resuscitation knowledge and skills	Paper instruments
Simulation practice of BMV	NeoNatalie Live app (or if NeoNatalie manikin used, paper instruments)
Key resuscitative actions, newborn respiratory status	LIVEBORN app
Newborn electrocardiographic tracing	Automatically transferred from NeoBeat to the LIVEBORN app via Bluetooth; may also be uploaded to the cloud using the NeoBeat app
Medical record abstraction	Table-based entry (e.g., KoboCollect)
Direct observation of debriefings	Paper instruments or tablet-based entry
Feasibility and acceptability of LIVEBORN (BIRTH-03)	Paper instruments
Facility culture and energy for work (BIRTH-08)	Paper instruments or tablet-based entry

6.2 RANDOMIZATION PROCEDURE

We will pair the four facilities based on enrollment rates (expected highest vs lowest as defined by the number of births). We will randomize to the intervention (i.e., real-time guidance or debriefing) within those pairs.

6.3 SAMPLE SIZE

Our sample size is based on the following assumptions: 63% of all babies are suctioned (based on our prior clinical trial with NeoBeat), the baseline total duration of suctioning among all babies is 55s (based on our prior clinical trial with NeoBeat), and we will observe 46% of births at the two largest facilities and 23% of births at the two smallest facilities using LIVEBORN. Given these assumptions and an anticipated 14,830 births during the study period, we will observe approximately 5,592 newborns. The proposed sample size of 5,592 newborns overall with approximately 1,864 occurring during the control phase and 3,728 occurring during the intervention phase allows for 80% power to detect a difference of 30s in total suctioning between the control and intervention phases assuming a standard deviation of 60s (Table 3). The ICC of 0.33 reflects the ICC we observed in our recent clinical trial of NeoBeat. It also allows for 80% power to detect a difference of 25s between real-time guidance and debriefing assuming a standard deviation of 60 (Table 3).

Table 3. Total sample size required for 80% power for 4 clusters and an ICC=0.33

Hypothesis 1 (1:2 ratio)				**Hypothesis 2**			
Mean difference in suctioning time (seconds) between control and intervention				***Mean difference in suctioning time (seconds) between study arms***			
Standard Deviation	**20**	**25**	**30**	**Standard Deviation**	**20**	**25**	**30**
40	1807	776	404	**40**	1437	638	316
60	8716	3674	1807	**60**	6940	2916	1437
80	27186	11297	5535	**80**	21462	8878	4365

At present, there are 61 nurse midwives employed across the four facilities. As such, we expect approximately 30 nurse midwives per study arm.

6.4 ANALYSIS

6.4.1 Analysis of Pilot Phase

During the pilot phase, we will compare each nurse midwife's knowledge and skill evaluation scores to the standard pass rate for each instrument. If any nurse midwife scores below the passing score on a particular evaluation, we will conduct additional training and have her re-take the evaluation until she achieves a passing score. We will analyze the frequency of LDHF practice sessions per midwife at the end of the pilot; if the average is less than once weekly, we will consider how to increase the frequency of practice moving into the control phase.

During small-scale testing of observing births with LIVEBORN, we will rapidly analyze data (including direct observations, semi-structured interviews, the percent of births observed with LIVEBORN, and the use of NeoBeat during resuscitations) and generate a summary report to support refinement of the strategy in the subsequent round. Recommendations for refining the strategy will be based on the percent of LIVEBORN observations achieved and the consistency of NeoBeat use.

6.4.2 Analysis of Control and Intervention Phases

Our primary hypothesis is that the duration of suctioning among all newborns will improve by 30s with LIVEBORN feedback (real-time guidance or debriefing) compared to recommended training and simulation practice alone. Our secondary hypothesis is that the duration of suctioning among all newborns will be 25s less in real-time guidance compared to debriefing.

For the clinical trial, we will evaluate the effectiveness of feedback with LIVEBORN on duration of suctioning by comparing the control and intervention periods. We will use a linear mixed model that includes fixed effects for study arm and time as well as their interaction. Because we cannot assume a linear trend over time, we will treat time as a categorical measure defined in 3-month intervals. We will account for correlation within cluster (i.e., facility) as well as within provider (i.e., nurse midwives) by including both factors as random effects. If the model fails to converge, we will explore treating facility as a fixed effect.

If feedback with LIVEBORN reduces duration of suctioning, we will compare the relative effectiveness of real-time guidance versus debriefing on duration of suctioning. We will estimate the difference in duration of suctioning between study arms using a similar model to that described for the primary hypothesis. As the test of the second hypothesis is conditional on observing an effect for the first hypothesis, we will not make additional adjustments for multiplicity. We will obtain relative risk between study arms and the associated 95% confidence intervals from log Binomial models using generalized estimating equations to account for the correlation of outcomes within cluster and provider. Secondary outcomes listed in section 5.2 will also be compared between real-time guidance and debriefing. Linear mixed models similar to the primary analyses will be used for continuous outcomes and log Binomial models will be used for dichotomous outcomes.

We will evaluate the feasibility and acceptability of both real-time guidance and debriefing using validated surveys. We will consider each of the strategies sufficiently feasible and acceptable if the median FIM and AIM scores are >12.

6.5 Dissemination of Findings

This trial will be registered at ClinicalTrials.gov and results information submitted in accordance to its policies. This will also be stated as part of the informed consent form. Data availability will follow guidelines of the funders and participating institutions.

7 Ethical Considerations

The University of North Carolina (UNC) and Kinshasa School of Public Health (KSPH) Institutional Review Boards (IRBs) will approve this study protocol prior to the start of human subjects research.

7.1 Informed Consent

7.1.1 Newborns

Newborns will be included in this study with a waiver of informed consent for medical record abstraction and collection of data relevant to the newborn's condition at and around birth with LIVEBORN and NeoBeat.

7.1.2 Nurse Midwives

We will seek informed consent of midwives in-person. To protect participant confidentially, we will conduct all research-related discussions and informed consent procedures in a private room. If a private room is not available, a designated area far enough away from other people such that they cannot hear the conversation will be used. We will obtain informed consent in French, the native language, using the IRB-approved consent form. We will explain the purpose and procedures for the study. We will give adequate opportunity for each potential participant to understand the consent form and ask questions.

Fair balance will be maintained while describing the risks and benefits of participation in the study. No undue pressure will be placed on the potential participant to enroll in the study. If the potential participant agrees to participate, the participant and the research staff will sign the informed consent form. Midwife participants will be provided a copy of the signed consent form, and the research staff will retain the original, signed form.

7.2 POTENTIAL RISKS TO PARTICIPANTS

7.2.1 Newborns

There are minimal risks to newborns in this study. There is a risk of breach of confidentiality. All data collected about newborns, including demographic and outcome data, and physiologic data (breathing status, HR) will be linked to the participant's unique study identification number. Identifiers in this data will include date of birth and date of death (when applicable). All data collected about newborns will be transmitted securely to the investigators per the procedures outlined in the manual of operations. The only link between the newborn's name and the study identification number will be the participant log. Data from this log will be maintained locally in a secure, locked location.

7.2.2 Nurse Midwives

There are minimal risks to nurse midwives in this study. There is a small risk of breach of confidentiality. Data on the resuscitation actions of nurse midwives will be collected through observation with LIVEBORN. All data collected about nurse midwives, including surveys and the data registered in LIVEBORN will be linked to the participant's unique study identification number. The only link between the nurse midwife's name and the study identification number will be the participant log. Data from this log will be maintained locally in a secure, locked location.

There is also a risk of social embarrassment from receiving feedback during or after performance with LIVEBORN. This risk is no greater than the risk of receiving feedback from a supervisor regarding resuscitation (and such feedback already occurs during typical clinical practice at the study facilities). Nevertheless, to mitigate this risk, we will train nurse midwives in how to create a safe and supportive environment for guidance prior to the intervention phase.

7.3 POTENTIAL BENEFITS TO PARTICIPANTS

7.3.1 Newborns

There is a strong body of literature demonstrating improved perinatal mortality with implementation of HBB.[8,60,61] Feedback may also improve resuscitation care, and thereby improve newborn outcomes. Therefore, there is a likely benefit to newborn participants in this study. Conclusions drawn from this study will benefit newborns in the future through better understanding of the impact of feedback on resuscitation care.

7.3.2 Nurse Midwives

HBB training and simulation practice have been demonstrated to improve resuscitation care.[60] Bedside feedback has also been demonstrated to improve cardiopulmonary resuscitation performance.[27,28,31-35,62-64] Therefore, improved skills in resuscitation care is a potential benefit for nurse midwives enrolled in this study. Conclusions drawn from this study will benefit nurse midwives in the future through better understanding of the impact of feedback on resuscitation care.

8 PROTOCOL DEVIATIONS

Protocol deviations are instances where procedures specified by the protocol are not carried out or are carried out improperly. For example, a protocol deviation may occur if a midwife enrolls and then withdraws, a newborn is enrolled who is not eligible. The Study Physician or Study Coordinator will complete a form (BIRTH-04 Protocol Deviation) within three days of any protocol deviation. The KSPH co-investigator will review all protocol deviations before they are transmitted to UNC. The Study Coordinator will ensure all completed protocol deviation forms are securely transmitted to UNC within one week of the deviation.

9 DATA SAFETY AND MONITORING

The intervention tested in this clinical trial, namely LIVEBORN feedback, is of minimal risk to participants. As such, we will focus on documentation of serious adverse events (SAEs), with additional documentation of social harms which are of special interest.

9.1 SERIOUS ADVERSE EVENTS

We do not expect any adverse events (AEs) or serious adverse events (SAEs) for nurse midwives during their study participation. We do not expect any AEs (including SAEs) *related to research participation* for newborns.

An AE will be defined as any untoward medical occurrence in a study participant including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the individual's participation in the research, whether or not considered related to participation in the research. AEs will be considered serious if they meet one or more of the following criteria:

1. Result in hospital admission (unless hospitalization is preplanned, i.e., for birth) or prolongation of existing hospitalization,
2. Are immediately life-threatening,
3. Cause significant, persistent, or permanent harm or disability, either physical or psychological,
4. Result in death (excluding fetal demise)

Congenital anomalies/birth defects and fetal deaths will not be documented as SAEs in this study as the intervention under study in this trial occurs after birth.

9.1.1 Monitoring for Serious Adverse Events

Research staff will monitor nurse midwives and newborns for AEs, including events related to data collection. If an AE is assessed as serious, research staff will notify the Study Physician or Study Coordinator who will proceed with documentation per section 9.1.2.

9.1.2 Documenting Serious Adverse Events

Neonatal death and neonatal encephalopathy are expected to temporally occur during study participation and are considered SAEs. These outcomes will be recorded as part of medical record abstraction, and additionally documented with the completion of an SAE form (BIRTH-05). We do not expect any SAEs for nurse midwives. The Study Physician or Study Coordinator will complete an SAE form for any unexpected SAEs occurring during the study period.

9.1.3 Reporting Serious Adverse Events

The Study Coordinator is responsible for reporting all SAEs that are probably or definitely related to the study intervention to the Principal Investigator (PI) or designee within 72 hours of site awareness. The PI or designee will review these on a rolling basis.

The PI is responsible to ensure that all SAEs that are both 1) unexpected and 2) definitely or probably related to the study intervention are reported to the UNC and KSPH IRBs as soon as possible, and no longer than within seven days of site awareness. The prepared report submitted to the IRB will also be submitted to NICHD within seven days of site awareness (with care to exclude any personal identifiers of participants). This documentation will be emailed to NICHDAdverseEventRep@mail.nih.gov with the subject line "Serious Adverse Event Notification" followed by the PI's name and grant number.

SAEs that are possibly related or not related to the study intervention will be transmitted via DMS per routine procedures. All SAEs will be reviewed in aggregate by the steering committee (see section 10.2) approximately quarterly, or more frequently if deemed appropriate by the PI. Based on these study-related SAEs, the PI and co-investigators will continuously assess the need for and facilitate a protocol amendment or study cessation.

9.2 SOCIAL HARMS

For nurse midwives, there is a risk of embarrassment from LIVEBORN feedback regarding resuscitation performance that could result in social harm. Because social harm related to feedback is of special interest to implementation of LIVEBORN in a variety of contexts, we will carefully monitor for and document social harms per the plan outlined in this section.

A social harm will be defined as a non-medical untoward consequence of study participation, including: difficulties in personal relationships, stigma, or discrimination from family or community.

9.2.1 Monitoring for Social Harms

Research staff will monitor nurse midwives for social harms related to their study participation Additionally, we will provide a secure location for study participants and any concerned by-standers to report social harms using BIRTH-06 Anonymous Reporting of Social Harms.

9.2.2 Documenting and Reporting Social Harms

Research staff will document all social harms they become aware of that are possibly, probably or definitely related to the intervention (BIRTH-07 Social Harms). They will check the anonymous reporting system on a weekly basis, and complete a BIRTH-07 form for each anonymous reporting form completed. BIRTH-06 forms will be destroyed locally after the relevant information is documented on a BIRTH-07 form. The Study Physician or Study Coordinator will review all BIRTH-07 forms prior to finalizing.

Any social harms that are definitely or probably related to study participation will be reported to the PI or designee within seven days of site awareness. The PI or designee will review these cases on a rolling basis. Additionally, all study-related social harms (including those possibly related) will be reviewed in aggregate by the steering committee (see section 10.2) approximately quarterly. Based on these study-related social harms, the PI and co-investigators will continuously assess the need for and facilitate a protocol amendment.

10 STUDY ORGANIZATION, COORDINATION AND ADMINISTRATION

10.1 DIVISION OF RESPONSIBILITIES

The study team will be composed of personnel from five institutions: UNC, KSPH, Laerdal Medical, Research Triangle Institute (RTI) International and Jhpiego. Responsibilities of UNC, KSPH, Laerdal Medical and RTI are detailed below. Jhpiego will participate in a consultative role on an as needed basis. Table 4 lists all key personnel for this study and their specific role. The sections that follow describe the responsibilities of each organization.

10.1.1 University of North Carolina at Chapel Hill

UNC will coordinate all communication between the partner institutions and lead the study. This includes leading the development of the study protocol and manual of operations, as well as data analyses and reporting. UNC will develop the data management system with support from Laerdal Medical, and oversee data cleaning. UNC will be responsible for coordinating resources with RTI and Laerdal Medical to ensure the dissemination plan is completed.

10.1.2 Kinshasa School of Public Health

KSPH will lead the execution of the study protocol. The Study Coordinator will be responsible to lead the execution of the study in the DRC with the assistance of a Study Physician. They will hire and train at least one study nurse per facility to supervise research activities and collect data. The Study Coordinator, Study Physician and study nurses will recruit and enroll all participants in the health facilities. They will conduct all facility preparatory activities. The Study Coordinator and Study Physician will coordinate and supervise data collection procedures to ensure accurate data collection and expedient data transmission and error resolution. The Study Coordinator and Study Physician will conduct study monitoring and quality assurance activities. The Study Coordinator and Study Physician will ensure participant

Table 4. Roles of key personnel

Key Personnel	Role
Jackie Patterson (UNC PI)	Lead development of study materials, analysis, publication Coordinate communication among partner organizations
Eric Mafuta (primary KSPH Co-I)	Partner in all aspects of development/implementation/evaluation Conduct focus group discussion and interviews
Daniel Ishoso (KSPH Study Coordinator)	Lead the execution of the study in the DRC as the Study Coordinator
UNC Project Lead	Assist the PI in the development of study materials Assist the PI in coordinating communication among partners
Ben Chi (UNC Co-I)	Mentor ESIs in developing study materials, analysis, publication
Antoinette Tshefu (KSPH Co-I)	Mentor ESIs in study implementation Facilitate conduct of study in the DRC
Tracy Nolen (RTI Co-I)	Conduct all statistical analyses
Helge Myklebust (Laerdal Medical Co-I)	Advise on implementation of LIVEBORN and NeoBeat
Joar Eilevstjønn, PhD (Laerdal Medical Co-I)	Design the data management system
Ingunn Haug, MSc (Laerdal Medical Co-I)	Advise on implementation of LIVEBORN
Patricia Gomez (Jhpiego Co-I)	Advise on intervention sustainability/scale-up

Elizabeth McClure (RTI Co-I)	Advise on data management system Advise on statistical analyses

ESI=Early Stage Investigator

confidentiality and safety, and report any protocol deviations, SAEs and social harms per the procedures outlined in this protocol and the manual of operations.

10.1.3 Research Triangle Institute

RTI will conduct all statistical analyses. They will provide input on study design, protocol development and the statistical analysis plan. They will prepare final analyses for presentations and publications, and support the PI in producing any interim reports to NICHD. As funds allow, they will assist with data sharing.

10.1.4 Laerdal Medical

Laerdal Medical will assist UNC in developing the data management system, including implementing a database with tablet-based entry. They will produce reports to support data cleaning over the course of the trial. They will manage the cloud server that houses data from the LIVEBORN app including NeoBeat HR data. They will also provide technical advice to KSPH to support implementation of LIVEBORN and NeoBeat. They will support the PI in execution of the dissemination plan.

10.2 COMMUNICATION

To ensure the adequacy of continuous communication among key personnel in this study, we will establish a study steering committee made up of the PI and all Co-Is, and led by Dr. Patterson (the PI). The committee will rely on telephone calls, email and internet-based conferencing such as Zoom for communication. During the development of the study design as well as implementation of the study protocol, we will hold approximately once monthly conference calls.

Additionally, Dr. Patterson will lead approximately weekly remote calls with the KSPH team and UNC project lead to supervise implementation of the study. She will conduct site visits in Kinshasa approximately once annually. She will also meet with DRC colleagues at US-based biannual meetings for the NICHD Global Network.

10.3 STUDY TIMELINE

We anticipate completing this study in 36 months, with the timeline of activities detailed in Table 5.

Table 5. Proposed timeline of BIRTH project activities

Activity	Sept -Nov '22	Dec '22-Feb '23	Mar-May '23	June-Aug '23	Sept-Nov '23	Dec '23-Feb '24	Mar-May '24	June -Aug '24	Sept-Nov '24	Dec '24-Feb '25	Mar-May '25	June-Aug '25
BIRTH trial protocol/IRB												
BIRTH trial MOP												
HBB/LIVEBORN obs training				(7)								
BIRTH trial pilot				(8)	(9)							
BIRTH trial control					(10, 11)		(3)					
BIRTH trial intervention							(4, 5)				(3)	
Feasibility and acceptability surveys											(3)	
Trial analysis, submission for publication											(4, 5)	

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