



STUDY PROTOCOL

REVISED **Limiting adverse birth outcomes in resource-limited settings (LABOR): protocol of a prospective intrapartum cohort study [version 2; peer review: 2 approved]**

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Abstract

Background: Each year, nearly 300,000 women and 5 million fetuses or neonates die during childbirth or shortly thereafter, a burden concentrated disproportionately in low- and middle-income countries. Identifying women and their fetuses at risk for intrapartum-related

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morbidity and death could facilitate early intervention.

Methods: The Limiting Adverse Birth Outcomes in Resource-Limited Settings (LABOR) Study is a multi-country, prospective, observational cohort designed to exhaustively document the course and outcomes of labor, delivery, and the immediate postpartum period in settings where adverse outcomes are frequent. The study is conducted at four hospitals across three countries in Ghana, India, and Zambia. We will enroll approximately 12,000 women at presentation to the hospital for delivery and follow them and their fetuses/newborns throughout their labor and delivery course, postpartum hospitalization, and up to 42 days thereafter. The co-primary outcomes are composites of maternal (death, hemorrhage, hypertensive disorders, infection) and fetal/neonatal adverse events (death, encephalopathy, sepsis) that may be attributed to the intrapartum period. The study collects extensive physiologic data through the use of physiologic sensors and employs medical scribes to document examination findings, diagnoses, medications, and other interventions in real time.

Discussion: The goal of this research is to produce a large, sharable dataset that can be used to build statistical algorithms to prospectively stratify parturients according to their risk of adverse outcomes. We anticipate this research will inform the development of new tools to reduce peripartum morbidity and mortality in low-resource settings.

Keywords

Labor, delivery, intrapartum, postpartum, adverse birth outcomes, machine learning

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REVISED Amendments from Version 1

We have clarified the study inclusion criteria and availability of study sensor data to clinical care providers. We also updated the study status to indicate that all enrollment and follow-up is now complete and that we did successfully transition fetal sensors in 2022.

Any further responses from the reviewers can be found at the end of the article

Introduction

Each year worldwide, nearly 300,000 women and over 5 million fetuses or neonates die during childbirth or shortly thereafter¹⁻⁴. The vast majority of this burden is borne by the world's poor; only a tiny fraction of these peripartum deaths occur outside low- and middle-income countries (LMICs)⁵. Estimates of the worldwide burden of perinatal death demonstrate that 22% of maternal deaths and 50% of stillbirths occur in the intrapartum period and that 26% of neonatal deaths can be attributed to intrapartum events^{4,6}. Better identification of women and fetuses at risk for intrapartum complications could lead to improved outcomes through early intervention.

The Limiting Adverse Birth Outcomes in Resource-Limited Settings (LABOR) Study is designed to exhaustively document the course and outcomes of hospitalization, labor, delivery, and the immediate postpartum period in settings where the occurrence of adverse outcomes is high. Using information obtained from this study, we seek to develop machine learning, deterministic, and statistical algorithms that prospectively stratify women and fetuses by their risk of adverse outcomes and that signal actionable intrapartum diagnoses. These novel algorithms will lay the groundwork for the development of a robust suite of tools to reduce intrapartum morbidity and mortality in low-resource settings.

Methods**Study design**

The LABOR Study is a multi-country, prospective, observational cohort study. It was initially designed to enroll a maximum of 15,000 mother-infant pairs but this figure was modified to 12,000 after recruitment was slowed by the SARS-CoV-2 pandemic at all sites. The study has been registered prospectively with clinicaltrials.gov under identifier NCT04102644 and with the Clinical Trial Registry of India under CTRI/2020/01/022589.

Women are screened for study participation at the time of presentation to the hospital for delivery and followed for 42 days after delivery. The study's co-primary outcomes are composites of incident maternal and fetal or neonatal adverse events that may be attributed to the intrapartum period. For the mother, the primary composite outcome includes death, hemorrhage, hypertensive disorders, or infection. For the fetus/newborn the primary composite outcome includes intrapartum stillbirth, neonatal death, encephalopathy, or sepsis. The LABOR Study has been designed following the guidelines outlined by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Figure 1)⁷.

The study includes a pilot phase of the first 500 mother-infant pairs enrolled at the Zambia site prior to full implementation at all sites. The primary objective of the pilot is to gain experience with study procedures and outcomes measurement, and apply lessons learned about optimal strategies for enhancing uptake, retention, data quality, and data ascertainment to the larger observational cohort.

Study execution is expected to take 5 years, including start-up and staff training (9 months), enrollment and delivery (up to 3 years), completion of follow-up (2 months), data cleaning (6 months), analysis (6 months), and dissemination of results (3 months).

Study setting

The LABOR Study is conducted on the inpatient antepartum, labor and delivery, and postpartum wards at four sites across three countries: Korle-Bu Teaching Hospital (KBTH) in Accra, Ghana; Fakir Mohan Medical College and Hospital (FMMCH) in Balasore, India; Jawaharlal Nehru Medical College (JNMC) in Belgaum, India; and Women and Newborn Hospital of the University Teaching Hospitals (WNH-UTH) in Lusaka, Zambia. The sites were chosen based on the following criteria: large volume of deliveries, high incidence of adverse birth outcomes, and demonstrated capacity to implement rigorous clinical research.

Study participants

Women seeking care at a study facility who meet the following inclusion criteria are eligible for participation: 1) maternal age of majority (18 years at all study sites); 2) intrauterine singleton pregnancy; 3) admission to hospital labor and delivery unit with plan for either (a) vaginal delivery or (b) cesarean delivery in the presence of signs/symptoms of parturition, elevated blood pressure, or fever; 4) willing and able to provide written informed consent; 5) willing to adhere to study procedures and provide locator information for follow-up. Women being admitted to the labor and delivery unit with a plan for cesarean delivery who have no signs or symptoms of parturition, no elevated blood pressure, and no fever are therefore excluded. We exclude women who have any condition (social or medical) that, in the opinion of study staff, would make participation unsafe or not feasible. All potential participants are assessed for eligibility and enrolled following provision of informed consent. Participants are then followed through labor, delivery, and discharge and at seven- and 42-day follow-up contacts (phone calls or in-person visits). Liveborn infants are enrolled at birth and followed through 42 days of life.

Study procedures**Sensitization**

Each study site conducts routine "sensitization" activities to educate community members and potential participants about the LABOR Study. Study staff meet with key stakeholders and hospital staff regularly to ensure smooth integration of study activities into provision of standard care at each study facility. Study staff also periodically provide health talks and written informational materials to women attending antenatal clinics in the catchment area of the study facilities so that potential

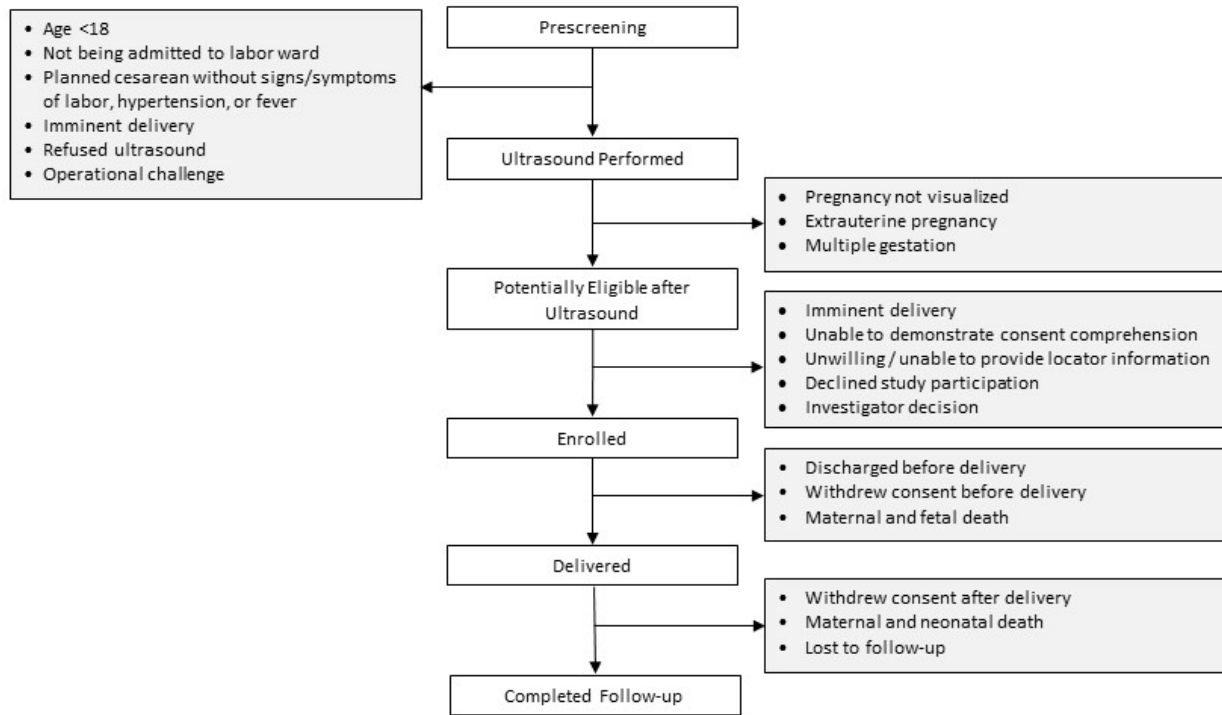


Figure 1. LABOR Study participant flowchart.

participants are informed about the study prior to presentation for labor and delivery.

Prescreening

To be able to compare women who enroll in the study with those who do not, staff record basic de-identified information about all women presenting for labor at participating sites, including maternal age, gravidity, parity, estimated gestational age, presenting symptoms, and any reasons for ineligibility for enrollment. Following prescreening, all women undergo an ultrasound performed by a certified sonographer or consultant obstetrician as part of standard care prior to study enrollment. The sonographer performs a general survey and fetal biometry measurements of biparietal diameter, head circumference, abdominal circumference, femur length, and transcerebellar diameter. While sonographers are encouraged to measure and record each structure twice, if not feasible due to advanced labor, descent in the maternal pelvis, or fetal cranial calcification, the minimum required biometry element is a single femur length measurement. Based on individual biometry measurements, the estimated fetal weight, due date, and gestational age as calculated by the ultrasound machine are documented in real time. Study sonographers then perform umbilical artery doppler velocimetry on all potential participants. The entire ultrasound examination, including abdominal sweeps collected as part of the general fetal survey, is electronically archived.

Screening and enrollment

Following prescreening assessment of basic eligibility criteria (e.g., maternal age, singleton pregnancy, admission to labor

ward, interest in study participation), potentially eligible women provide written informed consent in their preferred language. Before signing, a participant must demonstrate that she fully understands the information in the informed consent form by successfully completing a comprehension assessment. Participants provide separate consent for long-term storage of biological samples (detailed below) for possible future research testing not defined in the LABOR Study protocol. Participants may choose not to have these specimens stored for possible future research testing or withdraw their consent for long-term specimen storage at any time and remain in the study.

Study nurses collect information from consented participants about relevant maternal demographics, health and risk behaviors, and medical and obstetrical history in fixed case report forms. Research staff review the participant's medical records to abstract relevant antenatal care, medical comorbidities, prior ultrasound findings, and key laboratory results performed during pregnancy and in the hospital prior to study enrollment. LABOR Study staff perform a physical examination and collect peripheral blood, urine, and vaginal/rectal swabs for real-time testing and storage (Table 1).

Sensor placement

At enrollment, LABOR Study staff place physiologic sensors on each participant to collect maternal vital signs, maternal body position, fetal electrocardiogram, and uterine electromyogram. These data are not made available to providers for clinical care but are stored electronically for future correlation with adverse pregnancy outcomes. Continuous maternal vital signs are recorded by Sibel Health's ANNETM System that includes two

Table 1. Schedule of evaluations.

| | Enrollment | Labor | Delivery | Before discharge | 7 days after delivery | 42 days after delivery |
|--|------------|-------|----------|------------------|-----------------------|------------------------|
| Informed consent | • | | | | | |
| Collection / review of locator information | • | | | • | • | • |
| Medical chart abstraction | • | • | • | • | | |
| Demographic / behavioral assessment | • | | | | | |
| Maternal physical exam | • | | | | | |
| Ultrasound | • | | | | | |
| Maternal / fetal sensor placement | • | | | | | |
| Labor progress assessments | | • | | | | |
| Maternal / fetal sensor removal | | | | • | | |
| Maternal and fetal / neonatal outcomes assessment | | • | • | • | • | • |
| Neonatal physical exam | | | | • | | |
| Maternal point-of-care tests (HIV, syphilis, hemoglobin, urinalysis) | • | | | | | |
| Maternal chemistry | • | | | | | |
| Maternal hematology | • | | | • | | |
| Maternal lactate | • | | | | | |
| Cord blood lactate | | | • | | | |
| Neonatal blood culture (if NICU admission) | | | | • | | |
| Maternal vaginal / rectal swabs storage | • | | | | | |
| Maternal blood storage | • | | | • | | |
| Maternal urine storage | • | | | | | |
| Cord blood storage | | | • | | | |
| Neonatal DBS card storage | | | | • | | |
| Neonatal urine storage (if moderate or severe encephalopathy) | | | | • | | |

NICU, neonatal intensive care unit; DBS, dried blood spot

skin-mounted sensors placed on the maternal chest and finger. Fetal ECG signals are collected continuously by the MindChild Meridian M110 Fetal Monitoring System, an intrapartum fetal monitor that uses surface electrodes embedded in four patches placed on the maternal abdomen to detect fetal and maternal ECG signals and uterine muscle contraction signals^{8,9}. In early 2022, we transitioned to using Sibel Health's ANNE™ Emvryo fetal ECG sensor comprising 18 external electrodes placed on the maternal abdomen¹⁰. All ANNE™ devices include Bluetooth Low Energy capabilities and lithium-polymer batteries to allow use without a wired connection or external, steady electrical source.

Intrapartum procedures

Following enrollment, LABOR Study staff continuously collect data through labor, delivery, and immediately after delivery. To

accomplish this real-time task, we introduced study “scribes,” a cadre of data collection specialists tasked with collecting detailed information by direct observation, interrogation of clinical staff, and medical record abstraction. The scribes have no clinical role; on-site clinical care providers make all decisions and diagnoses regarding labor management in accordance with practice prevailing at each study site.

Scribes are positioned at participants' bedsides and enter data in real time into a tablet-based data management system, built using Dimagi's CommCare platform¹¹ and customized for use in the LABOR Study. Scribes are assigned up to three participants simultaneously, depending on volume and acuity of active intrapartum participants. Although real-time data collection is encouraged, when multiple events occur simultaneously or the scribe needs time to confirm observed

events, data may be entered retrospectively with a back-dated timestamp.

Throughout labor, delivery, and immediately postpartum, the scribes are responsible for recording detailed information about all actions performed, medications provided, and diagnoses made for each participant. Scribes document all actions carried out either by clinical staff or the participant herself, which may include assessments (e.g., cervical examination), procedures (e.g., amniotomy), or events (e.g., maternal pushing). Information recorded about medications administered includes name, route of administration, dose, and time administered. Scribes document all diagnoses made by on-site clinical care providers throughout labor, delivery, and immediately postpartum. Finally, they are responsible for ensuring continuous data collection from all study sensors and documenting any adjustments or interruptions.

During delivery and immediately postpartum, scribes are encouraged to prioritize real-time documentation of time and mode of delivery, time of cord clamping and placental delivery, estimated blood loss measured by a study-supplied calibrated drape (for vaginal deliveries), and any delivery complications. If scribes are present for cesarean delivery, they are additionally responsible for documenting the time and type of skin and uterine incisions. After delivery, scribes document neonatal vital status, Apgar scores, sex, birth weight, head circumference, and provision of any positive pressure ventilation.

Immediately after the umbilical cord is clamped and cut, a sample of umbilical venous blood is drawn and tested for lactate concentration on a point-of-care platform. Additional venous cord blood is also processed and stored for future testing.

Postpartum maternal and neonatal procedures

After transfer from the labor ward, LABOR Study staff closely track mother-infant pairs, visit each participant at least daily, and perform abstraction of maternal and neonatal medical charts. Study staff document maternal postpartum care, neonatal care, and final maternal and neonatal outcomes prior to hospital discharge. An additional maternal blood sample is collected once the mother is stabilized following transfer from the delivery room for immediate hematology analysis and storage for future testing.

Trained and certified study providers perform up to two neurological examinations to diagnose intrapartum-related neonatal encephalopathy for newborns weighing at least 1500 grams who meet any one of the following four physiologic criteria: ten-minute Apgar score <5, continued need for positive pressure ventilation at ten minutes of life, venous cord blood lactate >7mmol/L, or acute perinatal event, defined as intrapartum hemorrhage, umbilical cord prolapse, fetal distress as evidenced by an abnormal heart rate or pattern, or uterine rupture. The newborn neurological examination is based the modified Sarnat examination that evaluates level of consciousness, spontaneous movement, posture, tone, primitive reflexes, and the autonomic nervous system^{12,13}. For all

newborns diagnosed with either moderate or severe encephalopathy by neurological examination, urine specimens are collected and stored for future testing. One urine specimen is collected on the second day of life and another on day seven of life or discharge, whichever occurs first.

All newborns admitted to the neonatal intensive care unit within the first seven days of life are assessed for signs or symptoms of sepsis, and a blood culture is obtained (prior to antibiotics, if administered). Repeat blood cultures may be collected in cases of new, worsening, or recurrent signs or symptoms of sepsis during the first seven days of life. LABOR Study staff collect a dried blood spot card on all study newborns at 24 hours after delivery or discharge, whichever occurs first, to be stored for future analyses.

At discharge, LABOR Study staff complete a final review of the maternal and neonatal hospital course and reconcile key study diagnoses, medications, laboratory and radiographic diagnostic tests, and other interventions that occurred during labor, delivery, and the inpatient postpartum period. Study staff are responsible for confirming or correcting data recorded by scribes during the intrapartum and immediate postpartum periods and for adding any additional diagnoses and/or interventions that have occurred since delivery as documented in the medical record or in study chart notes. Finally, study staff categorize birth outcomes according to a modified rubric to assign a clinical delivery phenotype¹⁴.

Approximately seven and 42 days after delivery, LABOR Study staff contact participants by phone (or in person as needed) to assess maternal and neonatal status and interval course. Staff collect information about maternal and neonatal vital status and events since discharge, including signs and symptoms experienced, non-routine clinic or hospital visits attended, diagnoses made, and treatments received.

Laboratory procedures

All study samples are obtained from study participants by trained study staff according to approved standard operating procedures. Specimen transport, processing, storage, testing, and results reporting are conducted in accordance with Good Clinical Laboratory Practice (GCLP) standards¹⁵. Samples are processed according to the assay manufacturers' specifications by certified laboratory personnel. All relevant materials, including diagnostic specimens and infectious substances, are transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Potentially biohazardous waste is managed according to institutional, national, and other applicable regulations.

Whenever possible, maternal and neonatal blood samples are taken at the time of regularly scheduled clinical blood draws. Specimens are analyzed immediately as described in [Table 1](#) and stored at -80°C for later study-related analysis to identify inflammatory markers, metabolic analytes, proteins, hormones, transcripts, and infectious factors contributing to adverse birth outcomes.

Data management

The study database has four primary sources of data as follows (Figure 2): (1) fixed case report forms and real-time scribe data, managed via the CommCare system; (2) laboratory data, managed via CommCare and Lab Data Management Systems; (3) fetal and maternal physiologic sensor data, managed via a local server synchronized with cloud-based servers; and (4) ultrasound data, managed via a cloud-based server (Trice Imaging Inc, Del Mar, CA, USA). Data from each of these sources are automatically transferred to a secure, centralized server where they are queried, curated, and cleaned as needed. Key information from these sources is processed, synthesized, and presented on site-specific, custom-built R Shiny dashboards that are hosted on a secure, self-managed Shiny server and deployed on the web. Using data directly from the centralized server, dashboard metrics and visualizations are computed on demand without any required intermediate hand processing and available to authorized study staff at any time. Access to real-time study metrics allows the study operating center and site staff to track performance and identify challenges as they arise.

Data analysis and statistical plan

Study outcomes

The primary outcomes of the LABOR Study include a composite maternal outcome of potentially actionable incident adverse

events and a composite fetal / neonatal outcome of the same nature (Table 2). Secondary outcomes include the individual components of the two primary composite outcomes: maternal outcomes including maternal death, incident intrapartum hemorrhage, postpartum hemorrhage, incident hypertensive disorders (eclampsia, severe preeclampsia, preeclampsia, superimposed preeclampsia, severe gestational hypertension), and incident maternal infection (intrauterine inflammation or infection, endometritis), and fetal / neonatal outcomes including intrapartum stillbirth, neonatal death, encephalopathy, and sepsis. The LABOR Study distinguishes between prevalent conditions (those present at the time of enrollment) and incident conditions (those arising after enrollment). Although we identify and assess frequency of prevalent conditions, the primary focus of analytic approaches described below is the characterization and prediction of incident conditions.

Sample size

Because the incidence rates of certain complications of interest are small, we require a large sample size to observe sufficient numbers of each complication. During initial study planning, we calculated a sample size of 15,000 participants across three countries (four sites), with enrollment evenly distributed among the countries. However, with start-up and accrual delays owing to the SARS-CoV2 pandemic, we conducted a modified analysis to assess the impact of a reduced sample size of 12,000 on our key analytic goals.

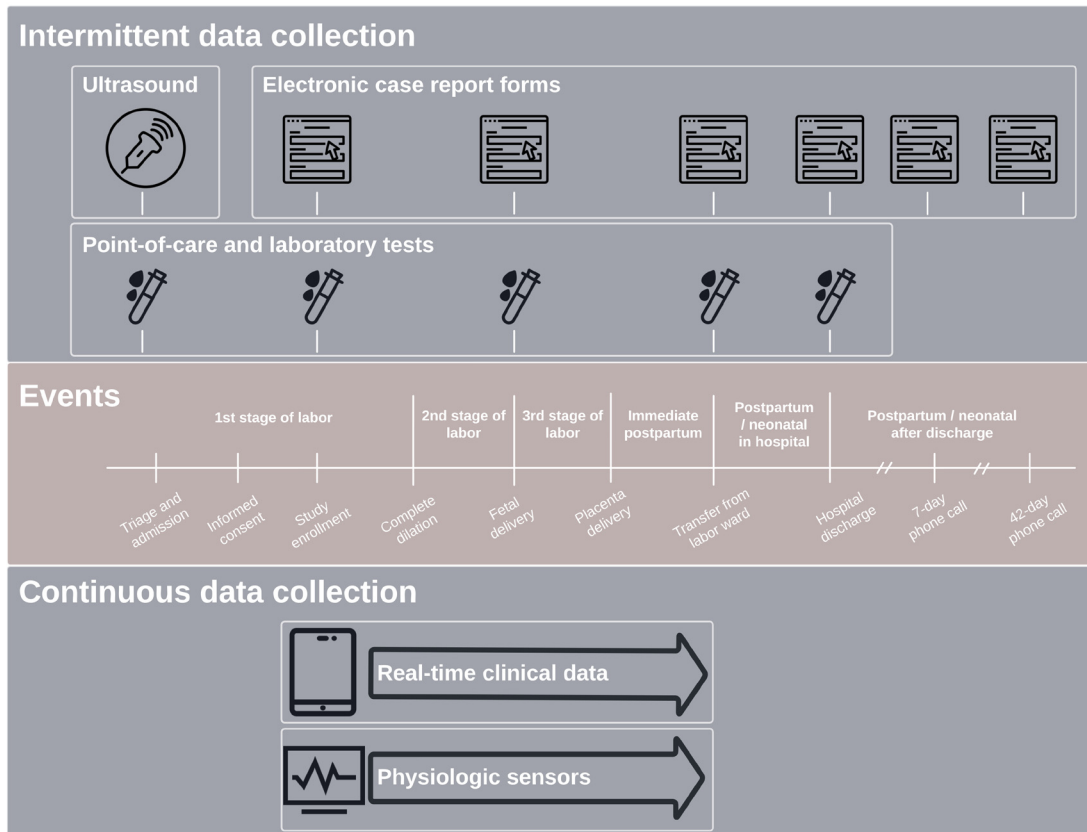


Figure 2. LABOR Study data collection.

Table 2. Study outcome definitions.

| Maternal Outcomes | |
|---|---|
| Maternal death | Death of a maternal participant after study enrollment and up to 42 days postpartum, irrespective of cause |
| Incident intrapartum hemorrhage | Intrapartum vaginal bleeding of ≥ 1000 mL of blood prior to delivery of the placenta |
| Postpartum hemorrhage | Blood loss of ≥ 1000 mL or any bleeding leading to an adverse event, regardless of mode of delivery, either within the 24 hours after delivery of the placenta (primary) or up to 42 days postpartum (secondary) |
| Incident eclampsia | New onset of tonic-clonic, focal, or multi-focal seizures in the absence of other causative conditions |
| Incident severe preeclampsia | New development of systolic blood pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg measured at least 4 hours apart in addition to proteinuria and at least one of the following severe features: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, new-onset cerebral or visual disturbances, or rise in systolic blood pressure to ≥ 160 mmHg or diastolic pressure to ≥ 110 mmHg |
| Incident preeclampsia | New development of systolic blood pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg measured at least 4 hours apart in addition to proteinuria in the absence of severe features described above |
| Incident superimposed preeclampsia | New development of preeclampsia as defined above in a woman with chronic hypertension |
| Incident severe gestational hypertension | New development of severe range blood pressure (i.e., ≥ 160 mmHg systolic pressure or ≥ 110 mmHg diastolic pressure) without proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual disturbances |
| Incident intrauterine inflammation or infection | Maternal fever and any of the following prior to delivery: fetal tachycardia, maternal leukocytosis, drainage of purulent fluid from cervical os |
| Endometritis | Presence of two or more of the following on any 2 of the first 10 days postpartum, exclusive of the first 24 hours and with no other recognized cause: maternal fever, abdominal pain, uterine tenderness, purulent drainage from uterus |
| Fetal / Neonatal Outcomes | |
| Intrapartum stillbirth | A stillborn fetus weighing at least 500g meeting all of the following criteria at birth: no heart rate, no respirations, absence of pulsation of the umbilical cord, and no definitive movement of voluntary muscles, and in which fetal heart tones were documented on the ultrasound performed at the time of LABOR Study enrollment |
| Neonatal death | Death of a live-born neonate within 28 days of birth |
| Neonatal encephalopathy | Live-born neonate weighing at least 1500g that meets one of the following four physiologic criteria: venous cord lactate > 7 mmol/L; 10 minute APGAR < 5 ; continued need for ventilation at ≥ 10 minutes of life; intrapartum hemorrhage, cord prolapse, severe fetal heart rate abnormality, or uterine rupture, and that demonstrates moderately or severely abnormal neurologic findings in at least three of the following six categories: spontaneous activity, posture, level of consciousness, tone, primitive reflexes, autonomic nervous system. |
| Neonatal sepsis | Live-born neonate exhibiting one or more signs of early-onset sepsis (i.e., convulsions, tachypnea, severe chest indrawing, nasal flaring, grunting, bulging fontanelle, pus draining from ear, umbilical redness extending to the skin, fever, low body temperature, many or severe skin pustules, lethargy / unconsciousness, or less than normal movement) with a positive blood culture (excluding contaminants) within the first seven days of life |

To do this, we performed a 2-part simulation study to assess our expected ability to (1) estimate risk and (2) estimate optimal decision rules. For (1), we assessed the anticipated precision with which we would be able to estimate risk for key outcomes using exact Poisson confidence intervals¹⁶. Basing our estimates on observed event rates in the first 500 participants in the study, we expect to estimate a rare event, one occurring in just 2% of the participants, with 95% confidence intervals with a half-width of 1.2%. For (2), using the first 500 observations in the study and 9 key covariates, we generated

simulation data sets by sampling with replacement from the observed covariates and constructing binary treatment decisions for each simulation record conditional on covariates. We also generated outcomes for each simulation record such that individual treatment effects exhibited heterogeneity dependent on interactions between the treatment and patient covariates. For each simulation data set, we estimated an optimal treatment rule that tailors treatment recommendations based on patient features. Across replications, we estimated the probability of correctly rejecting the null hypothesis that

there is no benefit of personalized decision-making when compared to completely randomized decision-making (i.e., a coin flip). With a true risk ratio of 1.17 and a sample size of 12,000 participants, our analysis indicates a 76% probability of correctly rejecting the null hypothesis. Our simulation results further indicate that an overall sample size of 12,000 yields sufficient power for estimating decision rules that, when used to recommend treatments, will reduce the probability of observing a bad outcome sufficiently close to the true optimal.

Statistical analysis

Descriptive analysis of baseline, intrapartum, and outcome variables. Common methods for descriptive statistics will be used to examine the distribution of key baseline factors, intrapartum events, and overall outcomes in the study population (e.g., frequencies for categorical variables and measures of centrality and dispersion for quantitative variables). These methods will also be used to examine unadjusted (crude) differences in the distribution of outcomes and intrapartum events by baseline factors. Key baseline factors will include maternal demographics, medical history and obstetrical risk factors, enrollment ultrasound, physical examination and laboratory values collected at admission or enrollment in the study. Intrapartum events will include time-varying variables related to the course of labor (e.g., cervical examinations), provider interventions (e.g., drugs, procedures), and continuous monitoring through fetal and maternal sensors.

Associations between baseline variables, interventions, and outcomes. Generalized linear models will be used to estimate the adjusted relative risk with 95% confidence interval of outcomes associated with baseline factors. Covariates (baseline factors) for inclusion in the multivariable models will be identified *a priori* based on clinical relevance and using causal directed acyclic graphs. We will start by fitting two separate models for binary outcome variables (yes/no) for the composite maternal and fetal / neonatal outcomes, respectively. If baseline factors of interest are found to be associated with the composite outcomes, we will fit models to each of the individual outcome components within each composite (maternal or fetal / neonatal). A similar modeling approach to that used for the composite and individual outcomes will be used to estimate associations between baseline factors (covariates) and key intrapartum interventions such as cesarean delivery.

Predictive models and risk stratification. We will develop and validate models to use baseline variables to predict the probability of each outcome. These predicted probabilities can be used to stratify patients by risk. Because of the expected high dimensionality of the data, we will consider the use of dimension reduction techniques such as deep learning autoencoders¹⁷, a nonlinear feature extraction tool using artificial neural networks, to reduce the dimension of baseline data prior to modeling, as well as, when appropriate, inclusion of regularization techniques such as elastic net¹⁸. Predictive models will be fit using multiple machine learning techniques such as random forests¹⁹, reinforcement learning trees²⁰, and kernel support vector machine²¹. Model selection and validation will be done within a cross-validation framework with models

fit using a training set, hyperparameters tuned using a validation set, and performance assessed on a testing set. For binary outcomes, model fit may be assessed using metrics such as accuracy, and for continuous outcomes, model fit may be assessed using metrics such as root mean squared error (RMSE). Key features identified in the predictive modeling will help us identify potential tailoring variables to be included in subsequent data-driven clinical decision support algorithms.

Signal processing and dimension reduction. The expected availability of multiple streams of physiological signals including maternal heart rate, contractions, and fetal heart rate in risk prediction models and clinical decision support algorithms is a unique opportunity. Yet, given the differences in the volume and velocity between these high-dimensional signal data and more standard clinical examination and laboratory data elements, some signal processing including possibly dimension reduction and feature extraction will be needed before the various types of data can be integrated into statistical learning models. A number of signal processing strategies are available; for example, Fourier decomposition methods may be used to analyze the nonlinear and non-stationary time series²², the aforementioned autoencoder²³ may be used to reduce signal dimensionality to a parsimonious class of features, and modern deep learning may be used on the raw signal directly to extract and construct novel, highly predictive features.

Finite horizon and infinite horizon dynamic treatment regimes. Beyond risk prediction, modern statistical precision medicine methods will be used to generate optimal, data-driven treatment recommendations. The statistical precision medicine framework formalizes the clinical decision-making process into a statistical model with baseline and time-evolving patient features, a sequence of key decision points, a set of feasible treatment options available at each decision point, and an outcome to optimize (i.e., either the maximization of a positive outcome or the minimization of a negative outcome). Framed within a rigorous causal framework, the goal is to learn from the data optimal dynamic treatment regimes (DTRs), which are sometimes referred to as individualized treatment regimes (ITRs). DTRs are a sequence of decision rules, one for each key decision point, that yield an optimal treatment recommendation given an individual patient's health status and history up to that decision point; they may take a multitude of forms, ranging from interpretable if-else decision lists to black box algorithms. Optimal DTRs are DTRs that, if followed, would improve outcomes on average across the population²⁴. Distinct from risk prediction, learning optimal DTRs is focused on improving decision-making and tailoring decisions to account for inter-patient heterogeneity.

We will assess the feasibility of analyzing a key decision or sequence of decisions using formal causal inference tools, including causal directed acyclic graphs and assessments of whether there are structural or practical positivity violations. If feasible, we will model key labor decisions in a Markov decision process (MDP) framework²⁵. For a given decision problem or sequence of related decisions, we will first analyze decision-making using a *finite-time horizon*

where decision time points are fixed, yielding one decision rule for each decision point that optimizes a targeted outcome across all of the decision recommendations. Optimal DTRs in this setting will be learned via off-policy, finite-time horizon reinforcement learning methods such as Q-learning²⁶ or simultaneous outcome weighted learning²⁷. When warranted by the decision problem at hand, we may then estimate an optimal DTR within an *infinite horizon* framework, where the decisions can be made recurrently with virtually no limit on the number of decision times. In this case, the estimated treatment regime provides real-time recommended actions based on both baseline and time-varying information rather than at pre-specified time points and is focused primarily on optimizing imminent outcomes. We will utilize reinforcement learning methods developed for infinite horizon problems such as V-learning²⁸ and greedy gradient Q-learning²⁹.

Missing data. As part of ongoing data quality assurance and control procedures, we monitor and promote high completion of key study variables before the end of follow-up, including baseline variables, intrapartum interventions, and variables used to define outcomes. In the analysis phase, we will investigate patterns of missingness and consider the use of multiple imputation or weighted estimation methods, as appropriate, to account for missing data when the proportion of participants missing data is more than 20%³⁰. We will also report complete case analyses alongside multiple imputation or weighted estimation to assess the impact of missing data.

Ethical considerations

The study is conducted according to international standards of Good Clinical Practice³¹. The protocol and informed consent documents are approved by properly constituted independent Ethics Committees (ECs) or Institutional Review Boards (IRBs) maintaining Federal Wide Assurances (FWA) with the Office for Human Research Protections (OHRP) at each site. All staff with participant contact receive training on the protection of human research participants prior to conducting any study activities and routinely thereafter³².

Participation in the study is voluntary. All study participants are provided a consent form describing the study and providing sufficient information for participants to make an informed decision about their participation in the study. LABOR Study consent forms are translated into local languages and back-translated into English to ensure accurate translation. Potential participants have the choice of undergoing consent in English (all sites); Hindi, Kannada, or Marathi (Belgaum, India); Bengali, Hindi, or Oriya (Balasore, India); Ewe, Ga, or Twi (Ghana); or Nyanja or Bemba (Zambia). Clinical study procedures are conducted according to local standards of routine care. Study staff inform women that they do not have to agree to participate in the study to receive care at the delivery facility even if investigators are affiliated with both the facility and the study.

Investigators make every reasonable effort to minimize risks to participants. We expect that participants in this

observational study will be exposed to minimal risk. Physical risks of participation include risks associated with venipuncture or finger prick, which are infrequent and minimized with use of proper technique. Collection of vaginal and rectal samples may also be associated with some discomfort. To reduce the risk of social or psychological harm, we explain the study in detail during the informed consent process and routinely remind participants that they do not have to answer questions that make them uncomfortable. To maintain participant confidentiality, all research-related discussions and informed consent procedures are conducted in a private room or area. All study data, laboratory specimens, and administrative forms are identified by a unique coded number. This unique number is scanned anytime data are captured within the password-protected study tablets. All databases are password-protected and accessible only to members of the study team.

The study has been approved by the following committees: University of North Carolina IRB, Chapel Hill, NC, USA; University of Ghana College of Health Sciences Ethical and Protocol Review Committee, Accra, Ghana; Korle Bu Teaching Hospital IRB, Accra, Ghana; Institutional Ethics Committee of KLE Academy of Higher Education and Research, Belgaum, Karnataka, India; Institutional Ethics Committee of Fakir Mohan Medical College and Hospital Balasore, Odisha, India; India Research and Ethics Committee, Directorate of Health Services, Odisha, India; Health Ministry Screening Committee of Government of India with Indian Council of Medical Research acting as its Secretariat; University of Zambia Biomedical Research Ethics Committee, Lusaka, Zambia; Zambia National Health Research Authority, Lusaka, Zambia.

Safety monitoring

At each study contact, study staff evaluate participants for social harms and adverse events. All adverse events occurring after study enrollment are assessed for seriousness and relatedness to study procedures. Study staff document and carefully monitor all serious adverse events occurring in participants whether or not they are related to study participation. The severity of any serious adverse events is graded using the National Institute of Health's Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Study staff are responsible for promptly reporting related adverse events or social harms to the site investigators and the overall study Principal Investigator, who determine if reporting to the appropriate ethics committees is required based on their guidelines.

Dissemination of findings

The LABOR Study team will disseminate findings to participants and key stakeholders at local dissemination events and globally at international conferences and in peer-reviewed journals. At the completion of this study, in accordance with the Bill and Melinda Gates Foundation Global Access requirements, research data from participants followed through pregnancy and the postpartum period will be curated and documented,

stripped of personal health information, and placed into the public domain. Additionally, the study team welcomes collaboration with others who could make use of intrapartum testing algorithms developed upon study completion. Knowledge generated from this study has the potential to contribute to the development of a suite of tools (which may include diagnostics, devices, and/or software) that can be deployed in low-resource healthcare facilities to substantially improve intrapartum outcomes in low-resource settings worldwide.

Study leadership and oversight

The LABOR Study is funded by the Bill and Melinda Gates Foundation and sponsored/coordinated by the University of North Carolina at Chapel Hill. The Management Team provides central technical and operations expertise to sites to ensure the successful implementation of the study and is responsible for developing the clinical protocol, training study staff, monitoring recruitment and retention, managing data quality, and ensuring regulatory compliance. The Steering Committee is led by the study Principal Investigator and comprises representatives from each participating site and additional ad hoc members selected for domain-specific knowledge. The Steering Committee advises on overall operations and manages all decisions concerning data analysis and interpretation, secondary analyses, and dissemination.

Study status

We completed participant follow-up at all sites in September 2022.

Discussion

Provision of quality obstetrical and neonatal health care is a complex matter that requires informed patients, trained providers, equipped and proximal facilities, timely diagnostics, an uninterrupted supply of essential treatments, and a coordinated strategy for all individual components to operate harmoniously³³. Obstetrical and neonatal services in resource-limited settings often lack some or all of these critical components. Algorithms that identify the maternal-fetal dyads at greatest risk for preventable intrapartum complications would allow the

targeting of limited resources toward those that need it most and are the most likely to benefit.

The overarching goal of our research is to develop new tools that can be deployed in low-resource healthcare facilities to improve intrapartum outcomes through better risk stratification, timely intervention or transfer to higher care, and earlier diagnosis. The first step toward this goal is to precisely characterize the incidence of adverse labor outcomes and their measurable antecedents in diverse populations while carefully documenting patterns of care. The data generated by this study will serve as a foundation for new discovery and development of novel technological approaches to substantially reduce adverse perinatal outcomes. With this study, we aim to create the largest, most extensively documented observational cohort of labor and delivery ever assembled.

Data availability

No data are associated with this article.

Acknowledgements

We thank our research participants and their families for providing data to this study. We additionally thank our research teams and the clinical care staff at each of the LABOR Study sites, including members of the LABOR Study Group in Ghana: Kwabena Agyapong-Osman, Robert Aidoo, Evelyn Amoah, Nathaniel Coleman, Ransford Kyeremeh, Constance Odonkor, Frank Ofori, Michael Opoku Ntrakwa, Rosemary Quartey, Alim Swarray-Deen; in India: Nihar Ranjan Behera, Sonali S Bijjargi, Sai Ravikiran Biri, Om Avishek Das, Sheetal U Harakuni, Basavaraj K Kocharagi, Namrata Misale, Vandana Mohapatra, Sujata Saraogi, Manjunath S Somannavar, Amruta Suryawanshi; and in Zambia: Florence Chilaisha, Gabriel Chipili, Chewe Lupunga, John Mwale, Humphrey Mwape, Rosa Mweemba, Michael Owino, Muyunda Pepino, and Ntazana Sindano. The team is especially grateful for the contributions of the late Mrs. Magda Mwale. Finally, we thank Drs. Sindura Ganapathi and Hilary Gammill for their support in conceptualizing this work.

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 **Soo Downe** 

THRIVE Centre, School of Community Health and Midwifery, University of Central Lancashire, Preston, UK

Thank you for the detailed responses to my comments. I am reassured that the findings of the study will be subject to extensive translation into clinical practice through trials and implementation science approaches, especially to confirm the feasibility, affordability, equity and effectiveness of using the proposed approach to personalised risk assessment. I am also reassured that some of the limitations addressed in both reviewers' comments, and acknowledged in the response will be addressed in the publication of the results of the study. On this basis, I am happy to approve the report.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Relevant to this proposal: Maternity care organisation and practice; Health systems research; Quality of maternity care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 17 October 2022

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**Soo Downe** 

THRIVE Centre, School of Community Health and Midwifery, University of Central Lancashire, Preston, UK

This is a protocol for a study that appears to be complete, based on the statement by the authors under the heading 'study status' that they expect to complete enrolment and follow up by the second quarter of 2022.

Overview

The protocol sets out plans for an ambitious and complex study to be run in multiple countries. It aims to identify maternal-fetal dyads at greatest risk of preventable intrapartum complications, to allow targetting of resources, with the hypothesis that this will improve outcomes for those most likely to benefit.

Comment

The ambition, reach, and attention to detail displayed in the protocol are highly laudable. Planned processes and procedures are clearly explained, and the addition of scribes in the labour ward is likely to address some of the problems of completeness and accuracy that other studies have encountered when trying to use routinely collected data (paper-based or online) for this kind of study.

I do have some caveats, and these relate to my scoring of 'partly' in relation to the fit between the research question and the study design. Most of these issues arise from the evidence that, while outcomes for mothers and babies are partly a function of their physical characteristics and interconnections, outcomes are also mediated by staff and organisational attitudes and behaviours, rules, guidelines, and procedures. For example, the most recent Cochrane review on the topic suggests routine use of EFM for low (and even high) risk women will result in higher CS rates than the use of intermittent monitoring, with no additional benefit to the baby long term¹. Some women labouring in organisations that routinely use EFM will therefore experience CS, and, potentially, post-surgical complications such as PPH, regardless of the intrinsic mother/baby dyad risks.

Similarly, some women labouring in sites where there is limited staff available will experience adverse events that will be prevented in sites where the staff/woman ratio is higher. Those who have further to travel, or who are handed over between institutions with minimal transfer of information may experience worse outcomes than those with similar clinical characteristics who live closer to a facility - and so on.

The issue here is that, if the locus of potential adverse outcome is only sited with the mother/fetus in any future algorithm for resource allocation, there may be a risk of both under or overdiagnosis, and, subsequently, both under and over-treatment - both of which could cause harm.

It may be that the statistical analysis will control for these organisational and human factors, which will then remove these concerns. However, even if that is the case, I was interested in this comment: '*Optimal DTRs are DTRs that, if followed, would improve outcomes on average across the population*'. This implies that the output from the study will not be personalised to individuals, but to a cluster of phenomena that might be associated with a certain outcome. The critical issue in

practice is then how sensitive and specific the tool is for particular individuals (i.e., how personalised it actually is) and to what extent both professional experts and service users will have the freedom to offer/accept/decline treatment based on the potential risk identified, as opposed to on actual manifestation of pathology.

It will be critical for implementation research to be undertaken with the tool to establish its acceptability, feasibility, affordability, equity, and possible unintended consequences or opportunity costs before it is irretrievably embedded into organisational and electronic systems, and, therefore, practice.

Additional comments and issues

1. I wasn't clear if the hospitals included in the study are typical for those to which the results are to be applied in the future. Women labour differently and have different outcomes in settings where they are well supported rather than not, especially if they have continuous labour companionship throughout labour². It would be good to know if the analysis will control for the different types of setting for the data collection, to see how this factors into the patterns emerging.
2. The inclusion criteria include the ability to provide '*written informed consent/locator information*'. The exclusion criteria encompass those with '*any social or medical condition that would make participation unsafe or not feasible*'. This does seem to have the potential to exclude women who are at most risk of the kinds of adverse outcomes of interest to the study (since being illiterate or living in dangerous social circumstances/having a severe medical condition is likely to be associated with the adverse outcome). Maternal or fetal deaths also seem to be excluded in the flow chart on p5, but they are included in the composite outcome. I'm not quite clear how this has operated in the study.
3. I couldn't tell from the protocol if women consented to the study antenatally or in labour. If in labour, I wasn't sure how the extensive data collection could be explained in a way that would ensure the woman really understood what she was signing up for.
4. How accurate are the following measures when done as a one-off?: *the estimated fetal weight, due date, and gestational age as calculated by the ultrasound machine are documented in real-time*
5. The protocol seems to suggest that the woman has (four or sixteen) sensors placed to measure fetal ECG and maternal vital signs from the time of enrolment (antenatally for some women?) until they are discharged from the hospital. I wasn't sure if there had been any consideration in the analysis of how having up to 16 sensors placed might impact on the freedom of movement of the mother in labour (and therefore on labour progress) even if they are wireless. I presume that the technology has been tested prior to the study to assess if it is unobtrusive, and robust (for example, in the exertion of labour, and the consequent rise in skin temperature/maternal sweating, do the sensors stay firmly fixed, or do staff have to keep re-siting them, interrupting the women's concentration on managing her labour?). After birth, if the woman is breastfeeding, it would be useful to know if this impacts the sensors/signals, and how the sensors might impact the success of breastfeeding, if at all. It would be helpful if the final report provides an assessment of the acceptability and feasibility of the sensors during labour and birth and the postpartum

period, especially if the proposal is that similar sensors might be used in routine practice in the future for women deemed to be high risk.

6. I note that the scribes are allocated up to three women simultaneously and that they are supposed to collect a large amount of data in real-time. I wonder if this is actually possible to do with accuracy and completeness. I imagine that this means that up to three women are labouring in one room. If this is indeed the environment in which these data are collected, this needs to be a caveat on the findings, since this kind of context may affect labour progress and outcome. It would be very helpful to have a description of the context and organisational labour room norms in the final report, to establish how far they may or may not have influenced the clinical progress and outcomes of labour and birth. This could include if women were upright and mobile or supine, or in lithotomy, if fundal pressure was used, and if the women had companionship, nutrition, pain relief, and respectful care as recommended by [WHO](#).
7. The primary outcome measure is a composite. While this makes sense at a population level, it doesn't really lend itself to a determination about what to do about individual risk. The problem with composite outcomes is that the aetiology and therefore treatment of different components of the composite are very different. While the individual components are included as secondary outcomes, it isn't clear if there will be sufficient statistical power to establish risk profiles for individuals with these specific outcomes.
8. The sample size calculation section states that the numbers anticipated could provide statistically significant findings for *'a rare event, one occurring in just 2% of the participants'*. Presumably then this doesn't include maternal death. It would, however, probably be sufficient for perinatal mortality in the included countries, though, as noted above, it isn't clear if these are exclusions for the study, despite the fact that they are included in the composite measure of outcome.

Dissemination plan

This looks reasonable. It is good to see the intention to share the findings with local participants and key stakeholders, and with academics at conferences and in journals. However, I can't see any plans for sharing with service user organisations more widely, or with national professional groups and policymakers. It might be useful to add this in to the plans going forward.

Statistical plan

I am not a statistical expert, so cannot comment on this part of the protocol.

Conclusion

As stated above, this is an important and ambitious study. It seems to be carefully designed, and it is very likely to produce a very large amount of useful data.

My main concerns are, firstly, about the extent to which assumptions are made that risk is only a function of the clinical characteristics of the mother/fetal dyad, without considering personal, social, and health care systems/organisational impacts on labour progress and outcome; and, secondly, the risks of the rapid introduction of any algorithm resulting from the study without proper assessment of the benefits and harms of implementation in the real world.

If both of these concerns are addressed in the final report and in future studies and practice, I am sure that the findings will be of critical importance in future maternity care.

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Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Relevant to this proposal: Maternity care organisation and practice; Health systems research; Quality of maternity care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 05 Dec 2022

Joan Price, University of North Carolina School of Medicine, Chapel Hill, USA

We greatly appreciate your careful review and commentary. Please find point-by-point responses to your questions and comments below.

I wasn't clear if the hospitals included in the study are typical for those to which the results are to be applied in the future. Women labour differently and have different outcomes in settings where they are well supported rather than not, especially if they have continuous labour companionship throughout labour. It would be good to know if the analysis will control for the different types of setting for the data collection, to see how this factors into the patterns emerging.

Each of the 4 study sites are hospitals based in low-resource urban areas. WNH-UTH, KBTH, and JNMC are tertiary teaching hospitals. FMMCH in Balasore is a busy second-level public hospital. We did not collect information about labor companionship since the WHO

guidance for encouraging a companion had not been universally implemented at the time of the study. We do plan to explore other differences in site data that may have been impacted by setting (see concluding paragraphs below).

The inclusion criteria include the ability to provide 'written informed consent'/locator information'. The exclusion criteria encompass those with 'any social or medical condition that would make participation unsafe or not feasible'. This does seem to have the potential to exclude women who are at most risk of the kinds of adverse outcomes of interest to the study (since being illiterate or living in dangerous social circumstances/having a severe medical condition is likely to be associated with the adverse outcome). Maternal or fetal deaths also seem to be excluded in the flow chart on p5, but they are included in the composite outcome. I'm not quite clear how this has operated in the study.

Requiring written informed consent introduces a limitation to the generalization of our dataset, a drawback that we will acknowledge when reporting results of the study. We attempt to approach all women presenting to the delivery room at each study site and offer them enrollment in the study based on preliminary eligibility (i.e., age, intent to deliver vaginally, singleton pregnancy) and interest in study participation. The most common reason that women are not able to provide informed consent is imminent delivery. Study staff were trained to identify individuals to serve as impartial witnesses during the consent process for any illiterate participants. Women with severe medical conditions are eligible to participate provided their condition did not interfere with the ability to provide consent (e.g., they were mentally disabled, unconscious, or receiving intensive care prior to delivery). The requirement to provide locator information is a telephone number only to allow for follow-up phone calls; participants were not required to provide an address.

Maternal or fetal deaths occurring after enrollment will be analyzed as study outcomes. We collect detailed information on all participants who died up to the time of death of both members of the mother-infant pair, who are then excluded from further follow-up activities.

I couldn't tell from the protocol if women consented to the study antenatally or in labour. If in labour, I wasn't sure how the extensive data collection could be explained in a way that would ensure the woman really understood what she was signing up for.

Most women consent while in labor. As stated above, some that are approached are too advanced for study consent to be feasible. To enhance comprehension of the consent form upon admission for labor and delivery, research staff routinely discuss the study with women receiving antenatal care who are likely to deliver at the study facilities. All participants are required to demonstrate understanding of the consent form based on a standardized tool administered prior to enrollment.

How accurate are the following measures when done as a one-off?: the estimated fetal weight, due date, and gestational age as calculated by the ultrasound machine are documented in real-time

We plan to compare estimated fetal weight on ultrasound to measured birthweight. Estimated due date (and gestational age at delivery) will be calculated using the established ACOG algorithm based on reported last menstrual period unless discrepant with the first ultrasound performed in pregnancy. We acknowledge that gestational age estimation with

ultrasound is associated with increasing error as pregnancy advances (although not as much as relying solely on last menstrual period).

The protocol seems to suggest that the woman has (four or sixteen) sensors placed to measure fetal ECG and maternal vital signs from the time of enrolment (antenatally for some women?) until they are discharged from the hospital. I wasn't sure if there had been any consideration in the analysis of how having up to 16 sensors placed might impact on the freedom of movement of the mother in labour (and therefore on labour progress) even if they are wireless. I presume that the technology has been tested prior to the study to assess if it is unobtrusive, and robust (for example, in the exertion of labour, and the consequent rise in skin temperature/maternal sweating, do the sensors stay firmly fixed, or do staff have to keep re-siting them, interrupting the women's concentration on managing her labour?). After birth, if the woman is breastfeeding, it would be useful to know if this impacts the sensors/signals, and how the sensors might impact the success of breastfeeding, if at all. It would be helpful if the final report provides an assessment of the acceptability and feasibility of the sensors during labour and birth and the postpartum period, especially if the proposal is that similar sensors might be used in routine practice in the future for women deemed to be high risk.

We agree, the possible impact of the sensors on a woman's concentration on managing her labor is an important consideration, but unfortunately, we did not enroll women without sensors so are unable to compare this between women with and without sensors during labor. We do plan to publish results of the feasibility of the sensors, which will include data on replacements as well as temporary and permanent removals and associated reasons. The sensors were removed shortly after delivery so did not interfere with breastfeeding. We will acknowledge this as a limitation of our study when results are published.

I note that the scribes are allocated up to three women simultaneously and that they are supposed to collect a large amount of data in real-time. I wonder if this is actually possible to do with accuracy and completeness. I imagine that this means that up to three women are labouring in one room. If this is indeed the environment in which these data are collected, this needs to be a caveat on the findings, since this kind of context may affect labour progress and outcome. It would be very helpful to have a description of the context and organisational labour room norms in the final report, to establish how far they may or may not have influenced the clinical progress and outcomes of labour and birth. This could include if women were upright and mobile or supine, or in lithotomy, if fundal pressure was used, and if the women had companionship, nutrition, pain relief, and respectful care as recommended by WHO.

We agree – the total volume of participants each scribe was assigned to and their relative acuity at the time will be important data to present in the final report as suggested. We did not (regrettably) explicitly collect individual data on companionship in the labor room and this is a noted limitation of our dataset, especially given the strong recent WHO recommendations. We do collect data on maternal position throughout the intrapartum period both through real-time scribe data and from the physiological sensors, which contain accelerometers. We will report these findings in future publications. Both fundal pressure and pain relief interventions are also collected in real-time by scribes at the bedside.

The primary outcome measure is a composite. While this makes sense at a population level, it doesn't really lend itself to a determination about what to do about individual risk. The problem with composite outcomes is that the aetiology and therefore treatment of different components of the composite are very different. While the individual components are included as secondary outcomes, it isn't clear if there will be sufficient statistical power to establish risk profiles for individuals with these specific outcomes.

Since optimal, tailored decision rules are focused on specific decisions, for these hypothesis-generating analyses, we anticipate defining optimality in terms of decision-specific outcomes. Decision-specific outcomes may or may not necessarily be the primary outcome measure, which is intended to capture a summary of the study rather than a targeted goal for a decision rule. With this in mind, our *a priori* sample size considerations for estimating optimal decision rules were based on a generic setting (a binary exposure, a mix of features types, and a binary outcome). We expect to have adequate sample size to learn optimal or near-optimal rules with high probability for a generic setting when the true risk ratio is as low as 1.7 for a binary treatment. From these analyses, we are not targeting the estimation of individual risk profiles, rather we are targeting optimal, tailored treatment decision support among heterogeneous individuals. This entails understanding how individuals with heterogeneous features under different treatments respond to those treatments in a rigorous causal framework and learning the optimal boundary between those who should get one treatment rather than another. Based on our extensive simulation studies, data from our study is likely to support finding such optimal boundaries with high probability.

The sample size calculation section states that the numbers anticipated could provide statistically significant findings for 'a rare event, one occurring in just 2% of the participants'. Presumably then this doesn't include maternal death. It would, however, probably be sufficient for perinatal mortality in the included countries, though, as noted above, it isn't clear if these are exclusions for the study, despite the fact that they are included in the composite measure of outcome.

Given our sample size, we expect to have adequate precision for outcomes as rare as 2%. This applies to both our composite maternal and neonatal outcomes and the individual maternal morbidity and neonatal morbidity and mortality outcomes used to estimate the composites. We expect maternal deaths to be much rarer than 2% and as such do not expect to have adequate precision to estimate the risk of maternal death as a single individual outcome. However, participants who experience maternal death will be kept in the analysis and contribute to the estimation of the primary maternal composite outcome.

Conclusion

We greatly appreciate your careful review and commentary. We will certainly include plans for sharing with service user organizations and national professional groups and policymakers as part of dissemination activities.

We agree that systemic factors including organizational and human factors mediate the translation of evidence into clinical practice. The difficulty with translation, generalizability,

and transportability is true for evidence generated through a precision analytic lens and also true for evidence generated through more traditional frameworks. Indeed, this issue is not unique to precision medicine.

We first clarify the role of (optimal) dynamic treatment regimes (DTRs) as evidence. Optimal DTR estimation is a hypothesis-generating goal, a strategy for identifying potential sequences of decision recommendations tailored to individuals that improve outcomes. As with any hypothesis, rigorous testing must be done before broadly applying it into clinical settings. This includes efficacy testing, e.g. a randomized control trial comparing the estimated optimal DTR to standard care. Finally, all evidence relies on thoughtful translation into clinical practice based on contextual feasibility, relevance, and acceptability; precision medicine and DTRs are not an exception, and we certainly would expect care providers and patients to apply precision medicine evidence as it makes sense in specific contexts.

The statistical precision medicine framework and DTRs allow for a form of data-driven decision support; as we write, they yield treatment recommendations given a set of features. We clarify that DTRs do not make recommendations based on clusters of phenomena associated with particular outcomes. That type of analysis falls within the domain of risk prediction, i.e. prognosis. In contrast, optimal DTR estimation is targeted towards optimal decision support, i.e. prescription of action or treatment, within a rigorous causal inference framework. Consequently, DTRs can delineate optimal treatments for different individuals even if they have the same level of risk. Analytically, this can be described as identifying phenotypic subgroups (heterogeneity) and how those subgroups interact with different feasible treatments, as opposed to how they associate with outcomes, at each decision point (see Kosorok and Laber (2019)¹ for a discussion of this difference). The analytic framework enables understanding optimal sequences of treatment that account for long-term outcomes (as opposed to myopic gains at the cost of long-term benefits overall) where each decision rule (one for each decision point) “takes in” individual features and “gives out” an optimal treatment recommendation based on the history and features of that particular individual. From a population perspective, improving treatment decisions for individuals yields population-level improvements (or at least no worse) in outcomes over the one-size-fits-all approach of following the same protocol for all individuals faced with the same decision without regard to individual features, history, and response to past treatment.

The precision medicine framework is well-poised to address some of the concerns regarding systemic factors that affect health outcomes. Because the framework leverages heterogeneity, structural differences between settings can be addressed through DTR estimation. With the substantial breadth of data collected in this study, which includes participants in 4 hospitals across 3 countries, we have a unique opportunity to leverage differences in setting in our planned analyses—that is, we can include site differences as part of algorithmic recommendations. Additionally, methods for transporting causal inferences from one setting to another is an active area of research with a number of methods and strategies already available for use.²

Of course, purely statistical methods are not a panacea, and are but a starting place for understanding the optimal use of precision medicine evidence at scale in real-world

settings. Bringing evidence to bear in complex systems falls into multiple domains including implementation science, systems science, statistical science, and clinical science, among others. These scientific domains must also incorporate key stakeholder engagement to optimize feasibility, relevance, acceptability, algorithmic fairness, equity, access, and to minimize potential harms. One strategy for this type of engagement is systems-aligned precision medicine, a general framework for embedding a systems lens to the translation of precision medicine evidence to clinical contexts.³ As we move forward, we certainly intend to bring a systems-aware lens to the application of any hypothesis generated from our analyses and carefully test our hypotheses before deploying any decision support tool at scale. The data we have generated from this study and our planned analyses are a starting point along the path of clinical decision support tools from optimal precision treatment algorithms towards scaled implementation.

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Competing Interests: None to declare.

Reviewer Report 06 September 2022

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G. Justus Hofmeyr 

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This paper describes the study protocol for a large, multi-country observational study focused on risk factors, interventions, and outcomes related to labour and the early postpartum period. A unique feature is detailed blinded physiological data acquisition, which in my opinion has the potential to provide important information. The planned statistical analysis is complex - I am not familiar with many of the statistical procedures and therefore not able to comment on them.

The following suggested additional information may be of interest to readers:

1. What clinical fetal monitoring unblinded to caregivers has been employed?

2. Has information been collected on the presence of childbirth companions, which may impact several of the outcomes being measured, such as low Apgar scores?
3. Has information been collected on maternal position, particularly the supine position during the second stage of labour, and will it be possible to relate maternal position to the physiological data collected (or to impute maternal position from the data provided by the sensors)?
4. Were partographs used for guiding labor management, and if so which design of partograph?
5. Were clinical management protocols in use? If so, some information on the protocols would be useful.
6. It would be useful to update certain statements, for example, whether recruitment, which is due to have been completed, has indeed been completed, and whether certain proposed changes in the technology available did in fact take place.
7. Study participants: the phrase: "3) admission to hospital labor and delivery unit with plan for either (a) vaginal delivery or (b) cesarean delivery in the presence of signs/symptoms of parturition, elevated blood pressure, or fever;" is not very clear - perhaps it could be written more precisely.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: General obstetrics including hypertensive disorders, postpartum hemorrhage and intrapartum care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 05 Dec 2022

Joan Price, University of North Carolina School of Medicine, Chapel Hill, USA

Thank you for your careful review and for approving our manuscript for publication. Please

see point-by-point responses to your questions and comments below.

What clinical fetal monitoring unblinded to caregivers has been employed?

Standard-of-care fetal monitoring at each of our four sites relies on intermittent monitoring by fetoscope or by handheld Doppler. Periodically, high-risk cases are monitored by continuous monitoring primarily at the Belgaum site. Study sensors were not intended for clinical care, so no sensor data was provided to caregivers in real time. See revised manuscript "sensor placement" page 6.

Has information been collected on the presence of childbirth companions, which may impact several of the outcomes being measured, such as low Apgar scores?

We did not collect this information, but anecdotally childbirth companions are rarely present at any of the study sites.

Has information been collected on maternal position, particularly the supine position during the second stage of labour, and will it be possible to relate maternal position to the physiological data collected (or to impute maternal position from the data provided by the sensors)?

We do collect information on maternal position (and position changes). We plan to validate positional data from the maternal sensors using real-time data collected by scribes at the bedside. See revised section on "sensor placement" page 6.

Were partographs used for guiding labor management, and if so which design of partograph?

Yes, partographs are regularly used to guide labor management at each site. At all four study sites, the modified WHO partograph is used. The most recent WHO Labour Care Guide has not yet been implemented at any of the study sites.

Were clinical management protocols in use? If so, some information on the protocols would be useful.

Clinical care at each site is guided by clinical protocols and algorithms for the management of various conditions such as hypertension, preeclampsia, antepartum hemorrhage, postpartum hemorrhage, etc. Our study scribes document care received (i.e., actions, diagnoses, medications) in real time, but do not assess providers' adherence to or variance from established clinical management protocols per se. We plan to investigate both variations in care between sites and variance from established protocols in future manuscripts, but think that a description of the various protocols at 4 different sites is beyond the scope of this protocol paper.

It would be useful to update certain statements, for example, whether recruitment, which is due to have been completed, has indeed been completed, and whether certain proposed changes in the technology available did in fact take place.

As we write, recruitment has indeed concluded, and we transitioned from Meridian to wireless Sibel fetal sensors as planned. These statements have been updated in the revised manuscript on pages 6 and 13.

Study participants: the phrase: "3) admission to hospital labor and delivery unit with

plan for either (a) vaginal delivery or (b) cesarean delivery in the presence of signs/symptoms of parturition, elevated blood pressure, or fever;" is not very clear - perhaps it could be written more precisely.

This is the eligibility criterion as written verbatim in the protocol. We have clarified this further in the manuscript.

Competing Interests: None to declare