NCT ID: 2019P000885

Document Date: September 26th 2021

Title: Wireless Physiologic Monitoring in Postpartum Women

Statistical Analysis Plan

Version 1.0
September 26, 2021

Adeline Boatin, PI
Massachusetts General Hospital/Harvard Medical School

Joseph Ngonzi, PI
Mbarara University of Science and Technology

NCT ID: 2019P000885

Document Date: September 26th 2021

Contents

Introduction 3

Study Objectives and Summary 3

General Analytic Considerations 3

- Data sources 3
- Test size and confidence levels 4
- Study size and Power 4

Exposure and Outcome Definitions 4

Analysis Cohorts and Datasets 5

Interim Monitoring 5

Analyses 5

- Baseline Data 5
- Participant Disposition and Retention 5
- Intervention: Monitoring Use and Monitoring Interruptions. 6
- Protocol Deviations 6
- Aim 1: To estimate the clinical effectiveness of wireless physiologic monitoring of women in the first 24 hours after cesarean delivery 6
- Aim 2: To evaluate the clinical adoption of wireless physiologic monitoring in a RLS using an implementation science approach using the RE-AIM Implementation framework 7

NCT ID: 2019P000885

Document Date: September 26th 2021

Introduction

This statistical analysis plan (SAP) details the statistical procedures to address the Primary and Secondary Objectives for the WIMS study.

Study Objectives and Summary

Protocol title:	Wireless Physiologic Monitoring Among Postpartum Women
Design:	Single site, prospective pragmatic type 2 hybrid effectiveness-implementation trial utilizing a quasi-experimental, interrupted time series with repeated on/off periods
Study arms:	Repeated on/off intervention-control periods in 2-week blocks. Intervention group to receive wireless monitoring, and Control group to receive standard of care.
Population:	Women aged 18 and older undergoing emergency cesarean delivery at MRRH
Sample size:	Approximately 1266 women (633 per arm); dependent on clinical volume during blocks
Study sites:	Mbarara Regional Referral Hospital, Mbarara
Aim 1:	To estimate the clinical effectiveness of wireless physiologic monitoring of women in the first 24 hours after cesarean delivery at a referral hospital in a RLS.
Aim 2:	To evaluate the clinical adoption of wireless physiologic monitoring in a RLS using an implementation science approach using the RE-AIM Implementation framework.
Aim 3:	To use qualitative methods to explore clinical adoption by doctors and acceptability of wireless physiologic monitoring among postpartum women in RLS and understand facilitators and barriers to uptake of wireless physiologic monitoring.

General Analytic Considerations

Data sources

Data are to be derived from the following:

1. Electronic data entry of questionnaire into REDCap
2. Electronic data entry of chart review into REDCap
3. Survey data from Midwives into Redcap
4. Vital sign data from Current Health devices
5. Alarm data from Current Health devices.

Test size and confidence levels

Analyses, including the primary analysis, will be based on two-sided α=0.05 level tests and 95% confidence intervals (CIs). No adjustment will be made for multiple comparisons.

Study size and Power

With 1266 enrolled participants, assuming an expected severe maternal outcome (SMO) rate of 13% in the control arm and intraclass correlation co-efficient of 0.01, will provide 80% power using a 2-sided α=0.05 to detect a difference of 5.7% in rate of SMO between the two groups.

Exposure and Outcome Definitions

Aim 1 exposure

- Allocation arm
    - Intervention block group for all eligible participants during that "on block" (regardless of actual monitoring receipt i.e., intention-to-treat).

Aim 1

Primary outcomes

- Composite of severe maternal outcome – one or more of the following outcomes represented in Table 1

Table 1: Severe Maternal Outcomes	
Outcome	**Definition/Measurement**
Death	Mortality occurring at any time point after delivery and prior to discharge
Clinical based near-miss criteria	
Acute cyanosis	Blue or purple coloration of the skin or mucous membranes due to low oxygen saturation
Gasping	Terminal respiratory pattern, the breath is convulsively and audibly caught.
Oliguria	Urinary output < 30 ml/hour for 4 hours or < 400 ml/24 hours non-responsive to fluids/diuretics
Failure to form clots	Bedside clotting test or absence of clotting from the IV site after 7 minutes
Prolonged unconsciousness	Complete or near-complete lack of responsiveness to external stimuli
Cardiac arrest	Sudden absence of pulse and loss of consciousness
Stroke	Neurological deficit of cerebrovascular cause persisting ≥ 24 hours
Uncontrollable fits	Refractory, persistent convulsions or status epilepticus
Total paralysis	Complete or partial paralysis of both sides of the body
Jaundice in the presence of pre-eclampsia	BP > 140/90 with proteinuria (> 1 + dipstick in ≥ 2 samples) and jaundice
Laboratory-based near miss criteria	
Acute severe azotemia	Creatinine > 300 mmol/l or > 3,5 mg/dl
Severe acute hyperbilirubinemia	Bilirubin > 100 µmol/l or > 6.0 mg/dl.
Severe acute thrombocytopenia	<50 000 platelets/ml
Management-based near-miss criteria	
Use of continuous vasoactive drugs	Uninterrupted infusion of dopamine, epinephrine, or norepinephrine
Hysterectomy	Surgical removal of the uterus following infection or hemorrhage
Massive transfusion	Transfusion of ≥ 5 units of blood
Intubation and ventilation not related to anesthesia	Placement of an endotracheal tube or ventilation for > 60 minutes purposes other than anesthesia
Dialysis for acute renal failure**	
Cardiopulmonary resuscitation	Emergency procedures including chest compressions and lung ventilation

Secondary outcomes

- Maternal Mortality ratio: Number of maternal deaths per 100,000 livebirths

Commented [BAA1]: Consider livebirths for only women included in the trial? Or consider livebirths for all women at the hospital

- Case fatality rate for
    - Hemorrhage – deaths/total number of hemorrhage cases
    - Hypertensive disorders of pregnancy- deaths/total number of HDP cases
    - Sepsis - deaths/total number of sepsis cases

Analysis Cohorts and Datasets

In the definitions below, a *cohort* refers to a particular set of participants and a *dataset* defines the time (or time intervals) contributed by participants in a cohort.

- **Screened cohort –** all participants with a screening CRF marked complete.
    - **Enrolled cohort –** subset of screened, who were eligible and enrolled i.e. received a study number
    - **Enrolled dataset –** analysis set of all baseline and follow-up data contributed by each participant in the enrolled cohort, regardless of compliance to group

- **Intervention cohort –** subset of enrolled cohort who are enrolled during an intervention time period
- **Control cohort –** subset of the enrolled cohort who were enrolled during the control block

Interim Monitoring

The DSMB will be responsible for review of operational and endpoint to assess the relative safety and relative effects of the interventions during the trial and monitor the overall conduct of the clinical trial.

The DSMB will provide recommendations about stopping or continuing the trial. The timing of formal interim analyses is yet to be determined. No formal stopping rules have been established.

Analyses

Baseline Data

Recruitment will be described for screened cohort including reasons for ineligibility among those screened.

Enrollment & Demographics by arm will be described for enrolled cohort. Summary statistics (e.g., frequencies, percentages, means, medians, inter-quartile range, minima and maxima) that are appropriate to the measurement scale will be used to describe baseline demographic, obstetric and medical history per tables developed prior to first interim analysis of data. No formal statistical testing will be performed to compare distributions of baseline characteristics between groups.

Commented [BAA2]: Should we do this to assess group balance?

Participant Disposition and Retention

The numbers of participants screened, enrolled, and allocated to each arm will be tabulated. A flow diagram will be provided which presents the numbers and percentages of participants contributing to the Primary Evaluable cohort. For any participant excluded from the cohort, the diagram will provide reasons for exclusion.

Intervention: Monitoring Use and Monitoring Interruptions.

Numbers of participants in the enrolled cohort who are eligible for wireless monitoring and receiving monitoring will be described. Numbers of participants with monitoring interruptions

- "Eligible for Monitoring" is defined as meeting criteria and with an allocated block for monitoring.
- "Receiving Monitoring" defined as using a current health device and having wireless vital sign monitoring data transmitted.
- "Time on intervention" calculated from reported monitoring start time to monitoring end time
- "Monitoring interruptions" - Percent of participants with monitoring interruption will be calculated out of those who received monitoring – defined as those who > 6 hours without monitoring data during the time on intervention.

Protocol Deviations

Protocol deviations will be summarized in frequency tables

Aim 1: To estimate the clinical effectiveness of wireless physiologic monitoring of women in the first 24 hours after cesarean delivery

Exposure	Intervention arm
Primary outcome	Severe Maternal Outcome
Endpoint	Discharge from hospital
Descriptive statistics:	Proportion of women with one or more SMO, overall and by arm.
Inferential statistics:	SMO will be statistically compared by arm using a Poisson model.

An intention to treat approach will be used to assess effectiveness. Thus, all women eligible for monitoring during an intervention arm including those who 1) declined consent 2) were missed from screening 3) were screened and not enrolled 4) enrolled but did not receive the intervention will be included in the intervention. The event rate for the primary and secondary outcomes will be calculated during the intervention and control time periods on all eligible women during those time periods. While intervention allocation was at the level of the two-week time period, the analysis will be at the individual patient level adjusting for clustering of observations within time periods. Using a logistic regression mixed effects model, with random effects to account for time block, we will compare the rate primary outcome between the intervention and control time periods.

Exploratory analyses will be used to determine if the intervention has a more significant effect in certain sub- groups of women (e.g. women <35, or women with more education). The interaction between study arm and comorbidities (i.e., HIV, hypertension, pulmonary, cardiac or kidney disease, malaria) will also be tested in logistic regression models. Subgroup effects will be reported if there is strong evidence of heterogeneity of intervention effect.

Commented [BAA3]: Intervention time periods will include women who
-Declined consent
-Were missed from screening
-Were screened and unable to enroll
-Enrolled but did not get the "full intervention"
-Screened and enrolled – deceased before monitoring
-Women ineligible due to language but those women will not be known in the control group.

Commented [BAA4]: Random effects for week using a mixed effects model
Vs GEE where you put in clustering or correlation

Commented [BAA5]: Account for missing data in control period
– impute for variables that are available and are independent for the intervention
-Use information from other people with the same arm
-Create a missing category and use that as one the variable
-Control for variables that are available in the chart

Aim 2: To evaluate the clinical adoption of wireless physiologic monitoring in a RLS using an implementation science approach using the RE-AIM Implementation framework

Descriptive statistics:
Descriptive statistics will be analyzed according to the RE-AIM Framework as below.

Reach: Proportion of target population that participated in the intervention

- *Percent of women with successful placement of biosensor after delivery*
  - Determined by number of women with monitoring data from CH/ Number of women enrolled in Redcap

- *Time to initiation of monitoring*
  - Time from delivery date & time until start time of monitoring as recorded by RA in enrollment log
  - Time from delivery date & time until start time of vital sign data received by current health
  - Time from delivery date and time until start time of valid vital sign data from current health.

- *Total length of time of monitoring*
  - Length of time women wore the monitor, calculated from start/stop times recorded by RAs (mean ± SD, median, IQR)
  - Length of time of vital sign data received by monitor, calculated from vital sign data received by CH (mean ± SD, median, IQR)
  - Length of time of valid vital sign data received by monitor, calculated from vital sign data received by CH after excluding implausible values.

- *Percent of women participating in monitoring for 24 hours*
  - Number of women wearing the monitor for ≥24 hours / Number of women enrolled
  - Number of women with vital sign data received by monitor for ≥24 hour/Number of women enrolled.

Efficacy: Success rate if implemented as in guidelines

- *Percent of women with HR, BP, RR and Tp available at least every 4 hours for 24 hours after delivery*
  - *Intent to treat:*
    - Number of women with HR (RR, Tp) measured every 4 hours for 24 hours/ Number of eligible women in block
    - Number of women with BP measured every 6 hours for 24 hours/Number of eligible women in block
  - *Actual allocation*
    - Number of women with HR (RR, Tp) measured every 4 hours for 24 hours/ Number of women with CH output
    - Number of women with BP measured every 6 hours for 24 hours/ Number of women with CH monitoring

Commented [BAA6]: Restrict to women in block vs women eligible

- *Percent of appropriate alerts sent (restricted to those with CH output)*
  - Number of women with alerts sent for HR (RR, Tp, BP)/ number of women with CH monitoring
  - Number of women with "appropriate" alerts sent for HR (RR, Tp, BP)/ number of women with CH monitoring. (*Appropriate defined as meeting the thresholds established by study protocol as in below)*

Predefined limits for clinician alerts	
Physiologic sign	**Cut off for alert**
Heart rate (beats per minute),	Mean >120 beats per minute for 10 minutes
Systolic blood pressure (mmHg), any	>160 or <70
Diastolic blood pressure (mmHg), any	>110 or <30
Temperature (C)	Mean ≥ 38C for 10 minutes
Respiratory rate (breaths per min)	Mean ≥ 30 breaths per minute for 10 minutes

- *Percent of alert receipt*
  - Number of alerts noted as received/Number of alerts sent. (Alerts received retrieved from midwife survey data on redcap using date/shift to collate; alerts sent from CH collated by date/shift.

Adoption: Proportion of practitioners adopting this intervention

- *Percent of eligible clinicians participating in wireless monitoring*
  - Midwives
    - Number of eligible midwives consenting/Number of eligible midwives
    - Number of midwives receiving phone/Number of eligible midwives scheduled
    - Number of midwives logging into system per shift/ Number of eligible midwives per shift (*Requires access to CH backend data on user logins and signing into on duty)*

- *Number of clinical actions in response to alerts – based on data from redcap surveys.*
  - Midwives
    - Time to review of alert
      - Proportion of alerts received reviewed <5 minutes, <15 mins, < 30 mins, 1 hr or ≥)
    - Proportion of patients assessed after report of an alarm (using end of shift survey data)
    - Proportion of patients with a clinical exam/procedure after report of receipt of an alarm (using end of shift survey data)
    - Proportion of patients with escalation in notification after report of receipt of an alarm (i.e., notification of someone else)

RE-AIM Implementation Science Framework			
Metric	**Dimension**	**Study Measure**	**Data source**
Implementation	Extent to which the intervention is	• Fidelity of implementation to the study protocol	• Documentation of any necessary adjustment to

	implemented in the real world		the protocol after study enrollment begins • Documentation of disruptions due to external factors
Maintenance	Sustainability of program over time	• Sustainability of reach, efficacy and adoption as measured by stability of measures over study period	• Above sources reviewed over the 12-month study period