Mobile WACh NEO: Mobile Solutions for Neonatal Health and Maternal Support

NCT04598165

STATISTICAL ANALYSIS PLAN

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1. STUDY SUMMARY AND AIMS

Rationale:

Globally, approximately half of the estimated 6.3 million under-5 deaths occur in the neonatal period (within the first 28 days of life) and 75% of neonatal mortality occurs in the first week of life. Most neonatal deaths can be averted by existing interventions that prevent and treat neonatal illness. The "three delays framework" identifies 3 critical delays in accessing care: 1) identifying illness and the decision to seek care, 2) reaching an appropriate facility, and 3) receiving adequate care. The first delay occurs beyond the reach of the clinic and is estimated to account for up to 80% of neonatal deaths. **A critical gap exists in supporting caregivers, typically mothers, to implement essential newborn care practices (ENC) at home, identify neonatal illness when it occurs, and seek timely clinic-based care.**

Two-way (interactive) short message service (SMS) offers an efficient way for mothers to remotely interact with a healthcare worker and receive real-time education, counseling, encouragement, and decisional guidance, without placing significant burden on resource-limited health systems. **We hypothesize that two-way SMS in late pregnancy and the neonatal period can reduce neonatal mortality by 1) supporting maternal implementation of ENC (early and exclusive breastfeeding, cord care, and thermal care), 2) improving identification of neonatal danger signs and care seeking, and 3) augmenting maternal social support and self-efficacy, and reducing depressive symptoms** (Figure)**.** We have developed a unique two-way SMS platform (Mobile WACh NEO, MWN) that rapidly and innovatively engages mothers in pregnancy and postpartum care. Our overarching aim is to determine the effect of MWN on neonatal mortality and understand the mechanisms by which this innovation impacts neonatal health. **We propose to determine the effect of MWN on neonatal mortality, ENC, care seeking, and maternal mental health in the first 6 weeks postpartum, in a 2-armed randomized controlled trial (RCT),** comparing MWN SMS versus no SMS control. Our specific aims are:

Design: A 2-arm, parallel assignment, unblinded, 1:1 randomized clinical trial (RCT) comparing the effects of MWN bidirectional SMS dialogue between participant and provider vs. control (no SMS) among Kenyan women.

Population: Pregnant women ≥14 years old and 28-36 weeks gestation.

Sites: Bondo District Hospital (Siaya County), Rachuonyo District Hospital (Homa Bay County), Mathare North City Council Clinic (Nairobi County), Riruta Health Centre (Nairobi County).

Sample Size: 5,000 pregnant women will be randomized (2,500 per arm)

Duration: Follow-up through 6 weeks postpartum.

Specific Aims:

Aim 1: To determine the effect of tailored, systematic two-way MWN SMS on neonatal mortality.
Hypothesis: Women randomized to MWN will have lower neonatal mortality than women randomized to control.

Aim 2: To determine the effect of MWN SMS on maternal implementation of ENC and care seeking behavior.

2a. To compare practices of early and exclusive breastfeeding, cord care and thermal care among mothers randomized to MWN versus control.

2b. To compare knowledge of infant danger signs and care seeking for neonatal illness among mothers randomized to MWN versus control.

Hypothesis: Implementation of ENC, knowledge of neonatal danger signs, and clinic attendance will be higher in mothers randomized to MWN than control.

Aim 3: To determine the effect of MWN SMS on longitudinal maternal social support, self-efficacy and depression among mothers randomized to MWN versus control.
Hypothesis: Maternal self-efficacy and social support will be higher and depression will be lower among women randomized to MWN than control.

2. STUDY ENDPOINTS

Primary study endpoints:

1. **Neonatal mortality** will be defined as death of a live-born infant within 28 days of birth, based on mother's report, verbal autopsy, or clinic records.

Secondary endpoints:

1. **Early neonatal mortality** will be defined as death of a live-born infant within 7 days of birth, based on mother's report, verbal autopsy, or clinic records.
2. **Initiation of early breastfeeding** will be defined as initiation of breastfeeding within the first hour of life, based on maternal self-report at 2-week postpartum study visit.
3. **Cessation of exclusive breastfeeding** in the first 6 weeks of life will be ascertained based on maternal self-report at the 2-week and 6-week visits.
4. **Bath** in the first 24 hours of life will be ascertained based on maternal self-report at the 2-week visit.
5. **Application of substances to cord** will be ascertained based on maternal self-report at the 2-week visit.
6. **Maternal provision of Kangaroo Mother Care (KMC)** will be defined as proportion of mothers with low birth-weight or preterm babies (<2500g or <37 weeks EGA at birth) who report the baby spent any time skin-to-skin with an adult on ≥10 of the first 14 days at home.
7. **Maternal knowledge of neonatal danger signs** will be defined as the number of the 8 neonatal danger signs correctly named at 2-week and 6-week visits.
8. **Appropriate care seeking** will be defined as the proportion of illness episodes with danger signs where the infant attended the clinic and/or where the infant was hospitalized independent of neonatal danger signs in the first 18 weeks of life (study follow-up period). Illness episodes are based on maternal self-report and only include the most recent illness episode reported at the 6-week visit or 2-week visit if 6-week data is unavailable.
9. **Elevated depressive symptoms** will be defined as a score ≥13 on the Edinburgh Postnatal Depression Scale (range 0-30) at 2-week and 6-week visits.
10. **Social support score** will be defined by MOS social support score (range 0-100) at 2-week and 6-week visits.
11. **Self-efficacy** will be defined by the Karitane Parenting Confidence Scale score (range 0-45) at 2-week and 6-week study visits.

Table 2.1 Summary of primary and secondary endpoints

Outcome	Indicator	Source	Timing
Primary outcome			
Neonatal mortality	Death during 1st 28 days of life	Questionnaire, clinic records; verbal autopsy	2 and 6 week visits, clinic record abstraction
Secondary outcomes			
Early neonatal mortality	Death during 1st 7 days of life	Questionnaire, clinic records; verbal autopsy	2 and 6 week visits, clinic record abstraction
Initiation of early breastfeeding	Breastfeeding in 1st hour of life	Questionnaire	2 week visit
Exclusive breastfeeding	Cessation of EBF in 1st 6 weeks of life	Questionnaire	2 and 6 week visits
Thermal care	Bath in 1st 24 hours of life	Questionnaire	2 week visit
Home provision of KMC	Any duration of skin-to-skin care on ≥10 of the first 14 days at home, among low birthweight or preterm infants	Questionnaire	2 week visit

Cord care	No application of substances to cord	Questionnaire	2 week visit
Maternal knowledge of neonatal danger signs	Number of the 8 danger signs or symptoms successfully named	Questionnaire	2 and 6 week visits
Appropriate care seeking	Proportion of illness episodes with danger signs where the infant attended the clinic and/ or where the infant was hospitalized regardless of danger signs reported during study follow-up	Questionnaire, clinic records	2 and 6 week visits, ongoing record abstraction
Depression	Score above diagnostic threshold (≥13) for Edinburgh Postnatal Depression Scale	Questionnaire	Baseline, 2 and 6 week visits
Social support	Score using MOS Social Support Survey	Questionnaire	Enrollment, 2 and 6 week visits
Self-efficacy	Score using Karitane Parenting Confidence Scale	Questionnaire	Baseline, 2 and 6 week visits

3.SAMPLE SIZE CONSIDERATIONS

Our endpoints will be compared between study arms using 3 types of statistical tests: comparison of proportions achieving the endpoint, comparison of hazard of the end-point by survival analysis, and comparison of continuous outcomes (see section 5.3). Secondary analyses will be adjusted for multiple comparisons using the Benjamini Hochberg method with a false discovery rate of 5%. In the power calculations below we use a conservative estimate with Bonferroni adjustment as an indication of the upper limit of our detectable effect sizes.

a. Analyses based on survival analysis

Assuming alpha=0.05, 2-sided test, 1:1 allocation ratio, with a sample size of 2,500 per arm, and 10% attrition, we will have ≥80% power to detect a Hazard Ratio (HR) of 0.53 in neonatal mortality, assuming mortality of 23 per 1000 births in the control arm. Assuming alpha=0.0045 (Bonferroni-adjusted for 11 tests) and 2-sided test, we will have ≥80% power to detect a difference of 90.0% vs. 93.1% continued exclusive breastfeeding to 6 weeks.

b. Analyses based on comparison of proportions

Assuming alpha=0.0045 (Bonferroni-adjusted for 11 tests), 2-sided test, 1:1 allocation ratio, with a sample size of 2,500 per arm, and 10% attrition, we will have ≥80% power to detect an change in early initiation of breastfeeding of 90.0% vs. 93.1%; bathing and application of substance to cord of 50.0% vs. 55.5%; elevated depression symptom prevalence of 19.0% vs. 14.5%. Assuming 15% of infants are born prematurely or have low birth weight, our analysis of KMC will have a sample size of 375 per arm. Assuming 10% attrition, alpha=0.0045 and 2-sided test, we will have ≥80% power to detect a change in KMC provision of 30.0% vs. 43.7%.

c. Analyses based on continuous variables

Assuming alpha=0.0045 (Bonferroni-adjusted for 11 tests), 2-sided test, 1:1 allocation ratio, with a sample size of 2,500 per arm, and 10% attrition, we will have ≥80% power to detect a difference in continuous scores of 0.11: 0.50 vs. 0.61 mean clinic visits, 3.00 vs. 3.11 mean danger signs named, and 2.50 vs. 2.61 mean social support score.

Table 3.1 Summary of detectable differences

Indicator	Outcomes (control)	Minimum detectable difference		
		Outcomes (intervention)	Absolute difference	Relative difference
Neonatal mortality per 1000 births[1]	25.0	13.8	11.2	0.55
	23.0	12.2	10.8	0.53
	20.0	10.0	10.0	0.50
Initiation of BF within 1h;	90.0%	93.1%	3.1%	1.03
EBF for 6 weeks[2]	80.0%	84.2%	4.2%	1.05
Application of substances to cord;	40.0%	45.4%	5.4%	1.14
Bath within 24h[2]	50.0%	55.5%	5.5%	1.11
Provision of KMC[2]	30.0%	43.7%	13.7%	1.46
	25.0%	38.2%	13.2%	1.53
Number of clinic visits in first 6 weeks[2]	0.50	0.61	0.11	1.22
	1.00	1.11	0.11	1.11
Number of danger signs correctly named[2]	3.00	3.11	0.11	1.04
	5.00	5.11	0.11	1.02
Maternal depression[2]	19.0%	14.5%	4.5%	0.76
Maternal social support score;	2.50	2.61	0.11	1.04
Maternal self-efficacy score (max 4.0)[2]	3.50	3.61	0.11	1.03

[1]α=0.05,[2]Adjusted α=0.0045, β=0.8, 2-sided tests

4. USE OF INTENTION-TO-TREAT AND PER-PROTOCOL ANALYSES

Analysis of primary outcomes will be by intention to treat (all participants).

After enrollment had begun, the study team became aware of other SMS health messaging interventions operating in the study area. On Aug 23, 2021, questions were added to the study visit questionnaire to ask participants if they were receiving SMS health messages from programs other than the Mobile WACh NEO study. Because the study was intended to evaluate the impact of the SMS program without contamination, the primary intention to treat analysis will be adjusted by whether participants ever reported receiving maternal health related SMS messages from other programs. Secondary sensitivity analysis will use per-protocol analysis, excluding participants who reported receiving SMS messages from other programs and excluding intervention participants who never successfully received any SMS from the study.

5. STATISTICAL ANALYSES

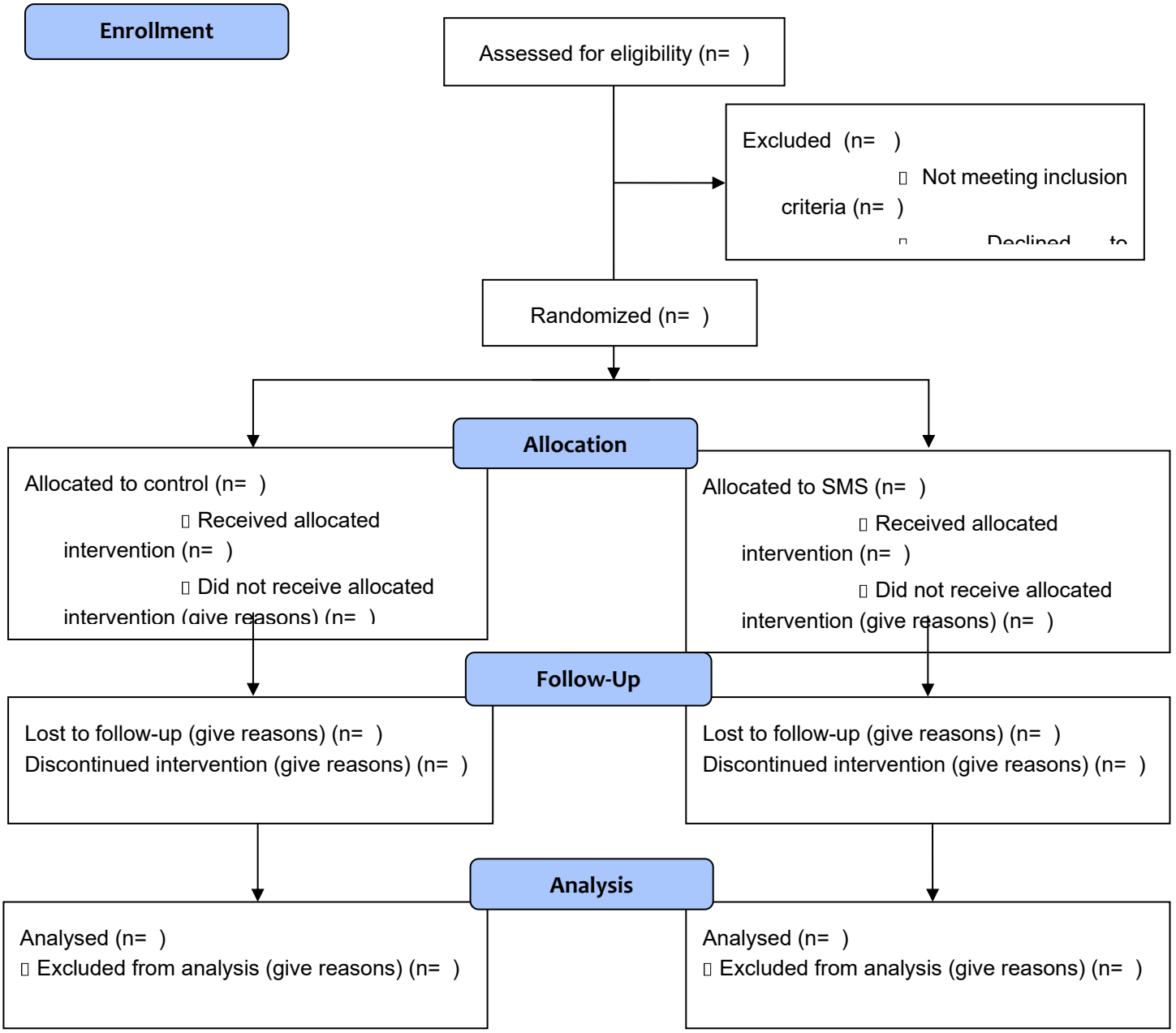
5.1 Study accrual

Per CONSORT guidelines, we will report the number of individuals who:

1. Underwent screening
2. Met inclusion criteria
3. Did not meet inclusion criteria (and reasons)
4. Enrolled in the study and were randomized
5. Treated as per study protocol

The number of individuals enrolled and randomized per study month will be presented in a figure by study arm. No formal statistical testing will be performed. See Figure 5.1.

Figure 5.1 – Trial profile



5.2 Baseline Characteristics

We will describe the distribution of baseline characteristics, using summary statistics appropriate for the measurement scale. We will present these summary statistics in tables both pooled and by study arm (see Table 5.2). To determine if the randomization resulted in balanced groups, baseline characteristics will be compared between randomization groups using Chi-square tests for categorical variables and the Kruskal-Wallis test for continuous variables. Any variables found to vary significantly at baseline will be included as adjustments in the primary analysis.

Table 5.1 Baseline characteristics: shell table

	Overall		Control		SMS	
	n (%) or median (IQR)					
Clinic:						
Facility 1						
Facility 2						
Facility 3						
Facility 4						
Facility 5						
Facility 6						
Sociodemographic						
Age (years)						
<12 years of education						
Crowding (≥3 people/room)						
Married / cohabiting						
Employed						
Shares phone						
Can read SMS unassisted						
Can write SMS unassisted						
Received SMS messages from other program						
Obstetric						
Primigravida						
Gestational age						
Mental health						
Elevated depressive symptoms						
Social support score						
Parenting confidence score						

5.3 Analysis of study endpoints

1. **Neonatal mortality**. Among live-born infants, the proportion who die in the first 28 days postpartum will be compared between arms by log-binomial regression. As a *secondary analysis* of this outcome, a Bayesian analysis will be conducted using Markov Chain Monte Carlo modeling to estimate the probability that the Mobile WACh NEO treatment effect exceeds a range of potential values. Models with a range of prior probabilities will be developed.
2. **Early neonatal mortality.** Among live-born infants, the proportion who die in the first 7 days postpartum will be compared between arms by log-binomial regression.
3. **Initiation of early breastfeeding.** Proportion of infants who initiate breastfeeding in the first hour of life will be compared between arms by log-binomial regression.
4. **Cessation of exclusive breastfeeding.** Time to first introduction of complementary foods will be compared between arms by Cox proportional hazards regression.
5. **Bath.** Proportion of infants who are bathed in the first 24 hours of life will be compared between arms by log-binomial regression.
6. **Application of substances to cord.** Proportion of infants who have any substance applied to their cord will be compared between arms by log-binomial regression.
7. **Maternal provision of Kangaroo Mother Care (KMC).** Among women whose babies were born at <37 weeks gestation or weighing <2500g, proportion of who provide KMC on ≥10 of the first 14 days that the baby is home will be compared by log-binomial regression.
8. **Maternal knowledge of neonatal danger signs.** The mean number of 8 neonatal danger signs correctly named by mothers at the 2-week and 6-week visits will be compared between arms by Poisson generalized estimating equations (GEE). Exploratory analyses will evaluate time-dependent effects by incorporating timepoint as an interaction term.
9. **Appropriate care seeking.** The proportion of illness episodes with danger signs where the infant attended the clinic and/or where the infant was hospitalized independent of neonatal danger signs in the first 18 weeks of life (study follow-up period). Illness episodes are based on maternal self-report and only include the most recent illness episode at the 6-week visit, or 2-week visit if data is unavailable at the 6-week visit. Differences in proportions will be compared between arms by log-binomial regression.
10. **Elevated depressive symptoms.** The proportion of mothers with score ≥13 on the Edinburgh Postnatal Depression Scale at the 2-week and 6-week visits will be compared between arms by log-binomial GEE. Exploratory analyses will evaluate time-dependent effects by incorporating timepoint as an interaction term.
11. **Social support score.** The transformed mean social support score (range 0-100) at the 2-week and 6-week visits will be compared between arms using linear GEE. Exploratory analyses will evaluate time-dependent effects by incorporating timepoint as an interaction term.
12. **Self-efficacy.** The summed parenting confidence score (0-45) at the 2-week and 6-week visit will be compared between arms using linear GEE. Exploratory analyses will evaluate time-dependent effects by incorporating timepoint as an interaction term.

Table 5.2 Summary of statistical analyses

Outcome	Indicator	Timing	Statistical Analysis
Primary outcome			
Neonatal mortality	Death during 1st 28 days of life	2 and 6 week visits, clinic record abstraction	Log-binomial regression
Secondary outcomes			
Early neonatal mortality	Death during 1st 7 days of life	2 and 6 week visits, clinic record abstraction	Log-binomial regression
Initiation of early breastfeeding	Breastfeeding in 1st hour of life	2 week visit	Log-binomial regression
Exclusive breastfeeding	Cessation of EBF in 1st 6 weeks of life	2 and 6 week visits	Cox proportional hazards
Thermal care	Bath in 1st 24 hours of life	2 week visit	Log-binomial regression
Cord care	No application of substances to cord	2 week visit	Log-binomial regression
Home provision of KMC	Any duration of skin-to-skin care on ≥10 of the first 14 days at home, among low birthweight or preterm infants	2 and 6 week visits	Log-binomial regression
Maternal knowledge of neonatal danger signs	Number of the 8 danger signs or symptoms successfully named	2 and 6 week visits	Poisson GEE
Appropriate care seeking	Proportion of illness episodes with danger signs where the infant attended the clinic and/ or where the infant was hospitalized regardless of danger signs reported in study follow-up	2 and 6 week visits, ongoing record abstraction	Log-binomial regression
Depression	Score above diagnostic threshold (≥13) for Edinburgh Postnatal Depression Scale	Baseline, 2 and 6 week visits	Log-binomial GEE
Social support	Score using MOS Social Support Survey	Enrollment, 2 and 6 week visits	Linear GEE
Self-efficacy	Score using Self-efficacy in Infant Care Scale	Baseline, 2 and 6 week visits	Linear GEE

Notes:

1. ***if any log-binomial regressions fail to converge, Poisson regression with robust standard errors will be used for all comparisons of proportions.***
2. ***If data needs to be imputed, the exclusive breastfeeding analysis will be conducted using Poisson regression with time offset instead of Cox regression, as this is asymptotically equivalent and easier to implement.***

Table 5.3 Study endpoints: shell table

	Overall	Control	SMS	p-value
Aim 1				
* Neonatal mortality (per 1000 live births)				
Aim 2				
* Early neonatal mortality (per 1000 live births)				
$ Time to introduction of complementary food				
* Breastfeeding initiated within 1 hour (%)				
* Bathed within 24 hours (%)				
* Substances applied to cord (%)				
* Provision of KMC among LBW/PTB infants (%)				
^ Number of danger signs identified				
+ Proportion of illness episodes with danger signs or hospitalization				
Aim 3				
+ Elevated depressive symptoms (%)				
# Social support score				
# Parenting self-efficacy score				

* Compared by log-binomial regression

$ Compared by Cox proportional hazards regression

* Compared by log-binomial regression

^ Compared by Poisson GEE

+ Compared by log-binomial GEE

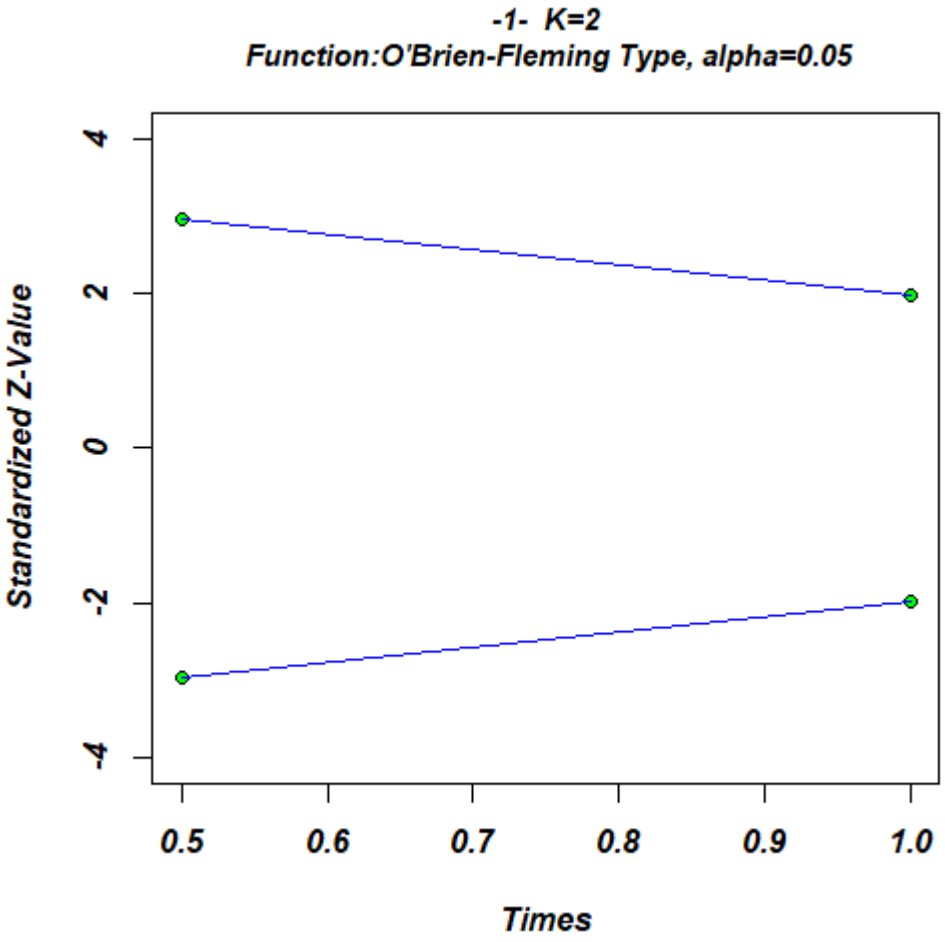
Compared by linear GEE

5.4 MISSING DATA

Based on the Mobile WACh NEO pilot, we expect 10% loss to follow-up between enrollment and the 6-week study visit. We anticipate that dyads who are lost to follow-up are more likely to be disengaged from care and have experienced adverse outcomes. We also anticipate missingness may differ by arm, with the intervention arm having higher retention. Sensitivity analyses will be conducted for the primary mortality outcome assuming all missing participants did or did not experience neonatal mortality. If missing data rates were unexpectedly appreciably higher than these rates, more nuanced sensitivity analyses would be considered, such as those that consider differing rates of neonatal mortality for the missing participants that differ by arm. Variables with >10% missingness will be multiply imputed by MICE.

5.4 INTERIM ANALYSIS

An interim analysis for neonatal mortality will be performed using O'Brien-Fleming boundaries for benefit and harm when 50% of expected person time has been accrued. The plot below shows the standardized z-value boundaries for interim monitoring.



5.5 SAFETY MONITORING

Adverse and severe adverse events, including social harms such as violence or breach of confidentiality, will be monitored, and unblinded results will be reviewed by the DSMB. The DSMB will make recommendations regarding any imbalances in safety outcomes.

Table 5.4 Adverse and severe adverse events: shell table

SAE #	PTIDNO	SAE description	Severity (Grade)	Onset date	Duration (days / unresolved)	Onset since randomization (days)	Relatedness to study

6. MODIFICATIONS TO ANALYSIS PLAN

Table 6.1 records modifications made to the analysis plan and their justification. Note changes made after December 2022 were after our final DSMB meeting and were not approved by the DSMB.

Table 6.1. Summary of modifications

Description of modification	Date of modification	Modified SAP version	Original approach	Updated approach	Justification
Outcome definition	8 October 2020	2.4		● Added early neonatal mortality as secondary outcome ● Added KMC as secondary outcome	DSMB recommendation
Mortality analysis approach	8 October 2020	2.4	Cox proportional hazards	● Log-binomial regression ● Secondary Bayesian approach	DSMB recommendation
Missing data approach	8 October 2020	2.4	None specified	Added approach	DSMB recommendation
Appropriate care-seeking outcome definition & analysis	23 December 2022	3.0	● Number of illness episodes where care was sought or baby was hospitalized ● Analyzed by Poisson regression	● Proportion of illness episodes with danger signs in which infant attended the clinic and/or infant was hospitalized independent of neonatal danger signs in the first 6 weeks of life ● Analyzed by log-binomial GEE	Data collection error resulted in care-seeking only being collected for the most recent illness episode.
Depression outcome definition	23 December 2022	3.0	Depression threshold cut-off listed as both 12 and 13	Clarified that cut-off was ≥13	An EPDS score of 13 is a commonly used cut-off in the literature and was specified in clinicaltrials.gov

Social support outcome definition	23 December 2022	3.0	Range of social support score values not specified	Clarified that this outcome will use the transformed mean scale (possible values 0-100) per the validated measure	
Parental self-efficacy outcome definition	23 December 2022	3.0	Range of self-efficacy score values not specified	Clarified that this outcome will use the summed score scale (possible values 0-45) per the validated measure. Also specified that score will only include 10 questions in original validated score; custom questions will be analyzed in exploratory analysis.	
Knowledge of neonatal danger signs outcome definition	31 January 2023	3.0	Definition specified 7 neonatal danger signs, unclear which ones were used	Definition now specifies 8 neonatal danger signs ● Difficulty feeding ● Weakness ● Hypothermia ● Fever ● Fast breathing ● Difficulty in breathing ● Convulsions ● Yellowness	Messages in intervention group discussed these 8 neonatal danger signs but did not mention the 9th sign listed in the CRF (sign of umbilical cord infection)
Education cut-off value	31 January 2023	3.0	Completed primary education used as cut-off	Completed secondary education used as cut-off	Given the high percentage of participants who completed primary education (>90%), this cut-off allows more discrimination comparing education between study arms
Intended pregnancy	6 February 2023	3.0	Compared proportion of pregnancies that were intended between arms	Will not include this variable in Table 1	Due to an error in skipping patterns, this question was not asked of primigravida individuals. Therefore, the data is not useful for comparing arms.

Use of intention-to-treat analysis	27 March 2023	3.2	Use intention-to-treat analysis on primary outcomes	Adjust for reported SMS messages from other programs in primary analysis Add secondary per-protocol analysis excluding individuals who reported receiving SMS messages from other programs	During the study, the study team became aware of other SMS health messaging interventions operating in the study area. This change to statistical analysis will adjust for contamination to the intervention by other SMS programs.
Other SMS messages	27 March 2023	3.2		Added receipt of SMS messages from another program to Table 1	This addition will describe how many individuals received SMS messages from other programs by arm.
Appropriate care-seeking outcome definition & analysis	20 April 2023	3.3	● Proportion of illness episodes with danger signs in which infant attended the clinic and/or infant was hospitalized independent of neonatal danger signs in the first 6 weeks of life Analyzed by log-binomial GEE	● Proportion of illness episodes with danger signs in which infant attended the clinic and/or infant was hospitalized independent of neonatal danger signs during the study period (up to 18 weeks). If data is unavailable at the 6-week visit, data from the 2-week visit will be used. Analyzed by log-binomial regression	Data collection error resulted in care-seeking only being collected for the most recent illness episode. 6-week visits could occur up to 18 weeks postpartum and we elected to include all data reported at study visits, regardless of when the care-seeking event occurred.
Approach to missing data	14 August 2023	3.4	Sensitivity analyses	Variables with >10% missingness will be imputed by multiple imputation by chained equations (MICE).	Two outcomes and one adjustment variable were found to have high levels of missingness. Multiple imputation has been shown to lead to less biased results than complete case analysis, and allows preservation of sample size.

Approach to exclusive breastfeeding cessation analysis	11 December 2023	3.5	Cox regression	For data imputed by MICE, use Poisson regression with time offset	Implementation of Cox regression with imputed data was unclear and Poisson regression is asymptotically equivalent.
Use of log-binomial vs Poisson regression	11 December 2023	3.5	Log-binomial regression	If any log-binomial regressions fail to converge, we will instead use Poisson regression with robust standard error	Log-binomial regressions frequently fail to converge. Poisson regression with robust standard errors yields asymptotic results.