STUDY PROTOCOL

V2.2 October 5, 2020

TITLE:

Mobile WACh NEO: Communication Empowering Mothers and Newborns

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1. LIST OF ABBREVIATIONS

ANC	Antenatal Care
CHW	Community Health Worker
ERC	Ethics Review Committee
FP	Family planning
HIV	Human Immunodeficiency Virus
HW	Health Worker
IDI	In-depth interview
IRB	Institutional Review Board
KNH	Kenyatta National Hospital
M&E	Monitoring and evaluation
MCH	Maternal and Child Health
MNCH	Maternal, newborn and child health
MOH	Ministry of Health
MWN	Mobile WACh NEO
MW	Mobile WACh (Mobile Solutions for Women's, Adolescent's and Child Health)
RCT	Randomized controlled trial
SMS	Short message service
SOP	Standard operating procedure
UoN	University of Nairobi
UW	University of Washington
WHO	World Health Organization

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Title of Proposal: Mobile WACh NEO: Mobile Solutions for Neonatal Health and Maternal Support
Dates: 01/06/2019-31/3/2024

5. SUMMARY

High-impact essential newborn care practices and interventions are available to support neonatal survival, but coverage remains a challenge in sub-Saharan Africa, where neonatal mortality is unacceptably high. Adherence to these practices and uptake of life-saving interventions requires that a mother understands neonatal care and illness and that she is supported to implement care. It is estimated that up to 80% of neonatal deaths occur as a result of delays in mothers' recognition of infant illness and decision to seek care. Two-way mobile health (mHealth) communication strategies can enable mothers to remotely interact with a healthcare worker (HCW) and receive real-time education, counseling, encouragement, motivation and decisional guidance to support neonatal health. We hypothesize that two-way SMS communication in late pregnancy and the neonatal period can prevent neonatal mortality by (1) supporting maternal implementation of essential newborn care (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. We have developed a unique two-way SMS platform (Mobile WACh) that combines automated bulk SMS messaging and dialogue with a HCW. We have adapted this approach for intensive neonatal support and evaluations (Mobile WACh-NEO). Mobile WACh NEO (MWN) enhances the benefits of SMS messaging by engaging mothers with SMS communication and bringing timely information and support - asking critical questions at crucial times in order to assess the needs and health of newborns. Our overarching aim is to determine the effect of Mobile WACh NEO on neonatal mortality and understand the mechanisms by which this innovation impacts neonatal health.

We will conduct a randomized controlled trial of the MWN intervention among 5000 women (2500 MWN arm, 2500 control arm) to determine the effect of MWN on neonatal mortality, essential newborn care, care seeking, and maternal mental health in the first 6 weeks postpartum. In AIM 1 we will determine the effect of Mobile WACh NEO on neonatal mortality, compared to no SMS control. In AIM 2, we will examine the effect of Mobile WACh NEO on maternal implementation of essential newborn care and care seeking behavior. In AIM 3 we will examine the effects of Mobile WACh NEO on maternal social support, self-efficacy and depression. Finally, we will explore the associations between maternal mental health, implementation of essential newborn care, neonatal care seeking and participant engagement by SMS.

This study will evaluate a novel intervention to address a crucial gap in supporting mothers to care for their neonates and seek care when needed, and has the potential to make a significant contribution to the World Health Organization's Every Newborn Action Plan to end preventable neonatal death and stillbirth.

6. INTRODUCTION/ BACKGROUND

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Prevention of Neonatal Deaths Remains a Challenge in Low-to-Middle Income Countries (LMICs)

Despite recent achievements in reducing child mortality, neonatal deaths remain high, accounting for 46% of all deaths in children under 5 worldwide (Figure 1) (2). The average annual rate reduction in under 5 mortality in 1990-2012 was 3.4%, compared to 2.1% in neonates (1st 28 days of life) (3). Neonatal morality in Kenya is reported to be 22.6 per 1000 live births (4), ranking among the countries with the highest number of neonatal deaths (~40,000) (5). Rates are higher among rural and urban poor. Achieving the World Health Organization's Every Newborn Action Plan (ENAP) target of ≤10 neonatal and stillbirths per 1000 live births (6) will require rapid scale-up of, and access to, effective, evidence-based interventions targeting the major causes of neonatal mortality.

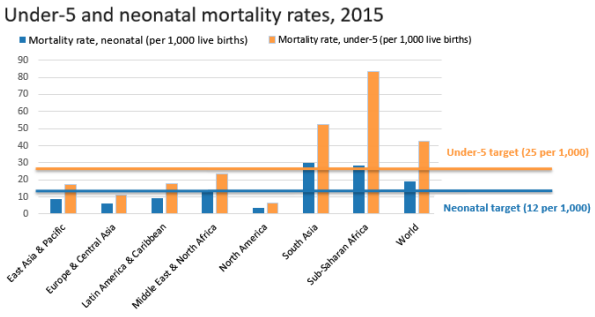

Figure 1: Comparison of under-5 and neonatal mortality rates by region, 2015.

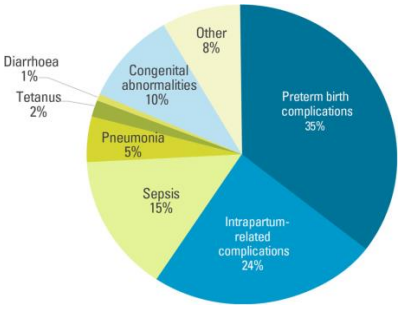

Figure 2: Causes of neonatal death, 2015 WHO (1)

Essential newborn practices have impact on adverse neonatal outcomes but are underutilized

Of the 2.8 million neonates who die each year, almost 75% die within the first week of life (7). Eighty percent of reported neonatal deaths are from complications of preterm birth (PTB), intrapartum deaths (including birth asphyxia) and serious neonatal infections (sepsis, meningitis, pneumonia and diarrhea) (Figure 2). For each of the major causes of deaths, evidence-based prevention and management solutions exist. **High coverage with existing interventions could reduce deaths from these common causes by 58% (preterm), 79% (intrapartum) and 84% (infection)** (8).

Families, particularly mothers, are vital for providing newborn care, especially after the first day of life when most babies are sent home. High-impact cost-effective, mother-centered, practices are available for newborn health including essential newborn care (ENC): early initiation of exclusive breastfeeding (EBF), hygienic cord care, and thermal control (6). Evidence from pooled data show early initiation of breastfeeding (within 1 hour of life) and EBF are independently associated with lower neonatal mortality (9). Clean cord care in the days following birth is effective in preventing cord infections (10), and neonatal mortality (11) mainly due to *Clostridium tetani*. Thermal care includes birth practices such as skin-to-skin contact with the mother, drying and wrapping immediately after birth, and delaying a bath for at least 24 hours. Appropriate thermal protection prevents hypothermia and associated morbidity and mortality particularly in the context of prematurity (12).

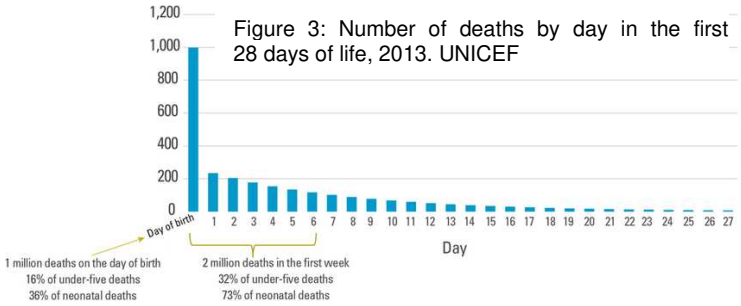

Figure 3: Number of deaths by day in the first 28 days of life, 2013. UNICEF

Although evidence for the efficacy of these interventions is substantial, coverage remains low. Large population-based surveys and smaller investigations in Uganda found sub-optimal practices of cord care, thermal protection and breastfeeding (13-15). Practice of appropriate cord care ranged from 31-39%, optimal thermal care from 42-67%, and appropriate neonatal feeding from 57-62%; women cited conflict between the recommended ENC and traditional beliefs and practices, especially delayed bathing and dry cord care. There is promising evidence that ENC practices may be accepted after behavior change communication messages from community health workers (CHWs) and facility-

based health care workers (HCWs) (16) but these interventions are both intermittent and costly, and do not address the problem of workforce constraints. A systematic assessment of 8 of 13 countries with the most neonatal deaths found significant bottlenecks across the health workforce, service delivery, financing and community ownership and partnership (17). All 8 countries, including Kenya, were found to have bottlenecks in community-based information, education and behavioral change communication strategies, as well as delays in seeking care.

Neonatal clinical care seeking is inadequate, often delayed, and requires more real-time support
Many newborns continue to die at home without health care services being sought (18). The reasons are multifactorial, at the societal, health system, and family levels. Strategic Objective 4 of the Every Newborn Action Plan is to "harness the power of parents, families and communities" by engaging them to seek care throughout pregnancy, birth and the first days and weeks of their children's lives. Improved identification and management of neonates with potentially life-threatening illness at home is critically needed to significantly reduce neonatal mortality (19, 20). **Decisions made within the household and the family's ability to reach care play a large part in determining neonatal outcomes.** The "three delays model", originally developed to understand maternal deaths (21), has been adapted to assess the missed opportunities leading to neonatal deaths. The model identifies delays in: (1) identifying illness and deciding to seek care, (2) reaching the health facility, and (3) in receiving quality care once a facility is reached. **Delays recognizing illness and deciding to seek care (delay 1) are a major contributor to neonatal and child deaths, up to 80%** (18, 19, 22, 23). In research from Kenya, Uganda, and Ethiopia, mothers had difficulty identifying serious illness in newborns, and they often did not seek care outside the home even when illness was recognized (24-26). Knowledge of danger signs is associated with fewer delays in identifying illness and seeking care (27). In addition, preventative postnatal care (PNC) is underutilized. In Kenya 50% of newborns in the richest households receive PNC within 2 days after birth, and 24% of those in the poorest households (4).

Figure 4: Three delays model for neonatal care

7. LITERATURE REVIEW

Maternal empowerment affects neonatal care and care seeking and can be supported by novel interventions
Maternal and neonatal health and well-being are inextricably linked. Maternal self-efficacy is an important determinant of positive parenting behaviors and infant attachment (28). A mother with low parenting self-efficacy may delay seeking care due to lack of confidence in making healthcare decisions, thus allowing the neonate's condition to worsen. Conversely, higher self-efficacy can lead to greater social and interpersonal connectedness, decision-making autonomy, and problem-solving. Although many factors determine parenting self-efficacy, maternal mental health (depression and anxiety) and social support are major predictors (28). In addition, maternal depression has been associated with adverse infant outcomes including PTB (29) low birth weight (LBW) (30), infant illness (31), poor social engagement (32) and developmental delay (33, 34) and is also predictive of poorer safe child practices (35). Even depressive symptoms alone, without a clear diagnosis, correlate with lower care seeking and preventive practices (36). It is not well understood how maternal depression affects neonatal survival, but it is plausible that parenting self-efficacy may affect neonatal outcomes. **Interventions that support maternal mental health by reducing depressive symptoms and increasing social support will bolster maternal/parental self-efficacy and improve neonatal outcomes.**

Community-based interventions work but are not accessible in real time
Clinic-based counselling during pregnancy and postpartum may increase uptake of effective practices and appropriate health care seeking (37), but high clinic volume and HCW shortages limit counselling time. Additionally, health concerns and challenges often occur between visits. Studies from LMICs

demonstrate that home visits and assessments by CHWs can improve maternal and neonatal outcomes (38). However, home visits are not 'on-call' and may miss critical periods when neonates become ill. Trials from South Asia also suggest that women's community groups improve ENC practices and neonatal mortality rates, although these groups may not be as effective in transient or dispersed populations and sufficient intervention coverage is a challenge (39, 40). Testing novel strategies in the form of accessible, acceptable digital interventions can strengthen the base of community care.

Mobile health (mHealth) interventions can provide support and information on-demand

mHealth tools, those that utilize mobile phones and other wireless technologies to support health, provide an attractive strategy to augment clinic-based care and efficiently connect households to support. More households in low-income countries own a mobile phone than have access to electricity or adequate sanitation (Figure 5) (41). The rate of mobile phone penetration in Kenya is over 88 per 100 inhabitants, with an estimated 37 million mobile phones in a national population of 43 million (42). **A World Bank report found that Kenyans living at the so-called "[economic] bottom of the pyramid" reported health information and communication as the service they would most like to receive with their mobile phones** (43). The ideal mHealth approach *increases efficiency rather than adding to healthcare workforce burden*.

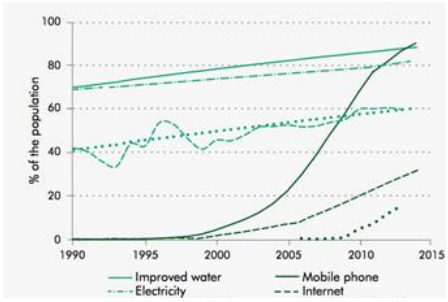

Figure 5: Digital technology spread in low-income countries

mHealth approaches such as short message service (SMS) messaging could provide guidance and support to mothers and families between clinic visits. There is evidence that mHealth can be used to educate, provide reminders for visits and medications, improve communication between HCWs and patients, and improve self-efficacy and depressive symptoms, all potentially leading to better outcomes (44-48). SMS programs for maternal, neonatal and child health (MNCH) have been implemented in South Africa, Bangladesh, India, Nigeria and the United States (49, 50). However, program efficacy data are lacking, and these programs are varied and often limited to education, encouragement and visit reminders rather than decision support (51, 52). There is some evidence that mHealth interventions improve antenatal care (ANC) attendance and skilled delivery uptake (53-56). Few studies have examined mHealth approaches for neonatal outcomes. One randomised controlled trial (RCT) observed a significant decrease in perinatal mortality with a combined unidirectional SMS and voucher intervention(57). These studies suggest mHealth may improve MNCH outcomes but more evidence is needed on efficacy, mechanisms, and best implementation approach. To our knowledge, no study has directly compared the effect of bidirectional SMS approaches, in which mothers can engage in interactive conversation with HCW by SMS, on neonatal outcomes. **We hypothesize that an interactive mHealth intervention has the potential to: 1) provide education and support with sustained practices of ENC, 2) provide education and decision support with identifying neonatal danger signs and seeking clinical care, and 3) provide emotional and social support for mothers to improve self-efficacy and decrease depressive symptoms.**

UW-Kenya mHealth Studies Human Centered Design Approach

Over the last 6 years, our collaborative team has developed an open-source human-computer hybrid communication platform, ***Mobile WACh*** (Mobile Solutions for Women's and Children's Health). This internet-based two-way SMS communication system is tailored to engage Kenyan mothers by SMS and improve maternal and child health (MCH) outcomes. The system contains a user interface designed for HCW management and patient tracking. **Through extensive formative testing with Kenyan mothers and HCWs, the Mobile WACh team has developed over 3000 personalized, actionable, encouraging, and time sensitive SMS messages.** Development of SMS messages in all studies was based on focus group discussions and interviews with the target population (58-60). The messaging platform was developed for management of SMS communications (61), with significant input from Kenyan nurses on features to improve usability and streamline workflow (Figure

6). The interface was designed to enable HCWs to **triage and counsel on potential medical conditions or concerns in a timely manner** (Figure 7). It includes features that motivate completion of tasks such as message responses, patient tracking updates, and coding of messaging for streamlined monitoring and evaluation. The system also enables collection of data on participant interaction (*paradata*) (62). Paradata from previous implementations of the Mobile WACh system (see section 3.3) have enabled us to understand effects of different messaging strategies (e.g. content, personalization, timing of messages, speed of response) to optimize the mHealth package. For example, we have analyzed messaging volume as a function of time and have found that participant messaging volume peaks in response to automated system messages. Interestingly, while many of the responses are related to the system message topics, many responses are on unrelated topics, which indicates that system messages can be used to trigger participant engagement, enabling HCWs to address issues without a clinic visit. The system is poised to reach large numbers of women with many flexible capabilities including different languages and diverse conditions (pregnancy, postpartum, infant growth and development, infant deaths, HIV). Currently the Mobile WACh platform is deployed in 8 sites in Kenya and has been used in 7 individual implementations to support mainly reproductive, maternal, newborn and child health (RMNCH) and HIV prevention and care in Kenya.

Preliminary studies: RCTs of Mobile WACh to improve MCH. Our collaborative research team has conducted 3 RCTs of interventions employing the Mobile WACh system (Table 1). The first Mobile WACh trial (NICHD, WRHR K12 PI: Unger) (63) was a 3-arm RCT to determine the effect of weekly 1-way (push) versus two-way (dialogue) SMS communication with a nurse versus control on uptake of maternal and neonatal services including facility delivery, EBF and postpartum contraception in the first 24 weeks postpartum (63). We found that both SMS intervention arms demonstrated higher rates of EBF through 10 and 16 weeks, and women in the two-way SMS arm were significantly more likely to adhere to recommendations to EBF through 24 weeks (Figure 8). The probability of contraceptive use by 16 weeks postpartum was significantly higher in both SMS groups than control. We received over 1100 messages from 83% of women in the two-way arm who engaged with the nurse (n=83). Infant health and breastfeeding were topics that compromised 20% of all messages received. Overall, there were 16 stillbirths and neonatal deaths (5%); 14 occurred prior to the first postpartum follow-up visit at 2 weeks. *There were fewer stillbirths and infant deaths in the two-way group compared to the control group* (3.1% versus 8.0%, p=0.21); although this was not significant, the study was not designed or powered to determine an effect on these outcomes.

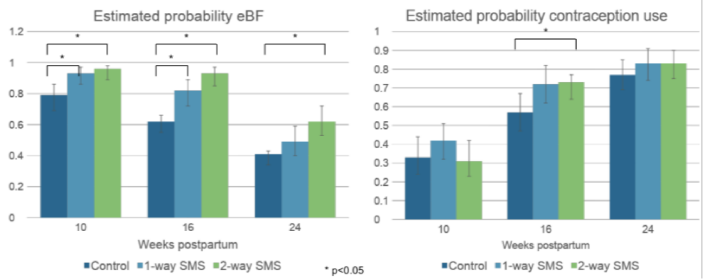

Figure 7: Effect of SMS interventions on primary outcomes among Mobile WACh participants (Unger BJOG 2018)

The success of the Mobile WACh approach was leveraged for 2 subsequent RCTs: Mobile WACh-X (NICHD, PI: John-Stewart) (64) and Mobile WACh-XY (Society for Family Planning, PI: Harrington) (58). Mobile WACh XY evaluated the effect of two-way SMS messaging on highly effective contraceptive (HEC) use at six months postpartum versus control among 260 Kenyan women. HEC use was significantly higher among women in the SMS group (69.9%) compared to controls (57.4%) with 94.6% of the 130 women receiving the intervention interacting with the intervention and sending 3188 messages (58). Mobile WACh-X is ongoing and expected to be completed in late 2019.

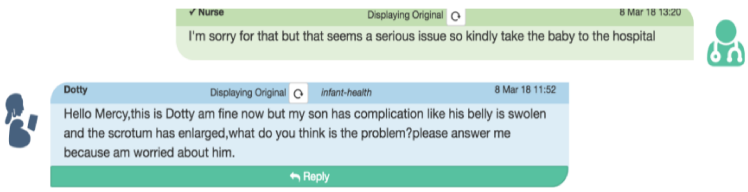

Figure 6: Mobile WACh messaging identifying a critically ill infant

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Table 1. UW-Kenya mHealth Studies Support the Reproductive Health Continuum

Investigator, location, year	Study Name	Number and Characteristics	Intervention	Study Design	Outcomes Measured	Results
Unger, Kenya 2013 (60, 61, 63, 65)	Mobile WACh	300 peripartum women and their infants	1-way SMS versus 2-way dialogue	RCT	Facility delivery contraption EBF	Improved early contraceptive uptake Improved EBF
John-Stewart, Kenya 2015 (59, 60, 64)	Mobile WACh X	875 HIV infected peripartum women and infants	1-way SMS versus 2-way dialogue	RCT	Retention ART Adherence Viral suppression Drug resistance Infant HIV	Ongoing
Harrington, Kenya 2016 (58)	Mobile WACh XY	260 postpartum women and male partners	2-way SMS	RCT	Highly effective contraceptive (HEC) use	Improved HEC use postpartum
Ronen, Kenya 2017	Vijana - SMART	110 HIV-infected adolescents	WhatsApp peer group intervention	Pilot	Retention ART adherence	Ongoing
Bhat, US 2016 (66)	DAWN	25 women with perinatal depression in collaborative care	2-way SMS	Pilot	Process outcomes	Use of SMS for depression support acceptable and feasible
Unger, Kenya 2016	Mobile WACh NEO	800 peripartum women and their infants	2-way SMS	Demonstration project	Process outcomes Facility delivery Contraception Neonatal mortality	Ongoing
John-Stewart, Kenya 2017	Mobile WACh PrIYA	300 young women and adolescent girls	2-way SMS	Demonstration project	Process outcomes PrEP adherence	Ongoing
Drake, Kenya 2017	mCube	1,000 adolescents and adult women	Smart logic 2-way SMS	Pilot	Process outcomes Contracepti	Ongoing

			for data collection		ve use Discontinuation Side effects	

Additionally, we have adapted Mobile WACh for 3 pilot projects: Mobile WACh NEO (Saving Lives at Birth, PI: Unger), Mobile WACh PrIYA (Pre-exposure prophylaxis implementation in young women and adolescents) (sub-aim) (DREAMS, PI: John-Stewart), and DAWN, a project for peripartum depression (sub-aim) (NIMH, PI: Bhat) (66). In each instance we have accrued extensive experience adapting the platform for use among vulnerable populations and handling sensitive information such SMS related to HIV management (59), depression (66) and adverse outcomes such as infant death (65).

Preliminary studies: mHealth and neonatal health

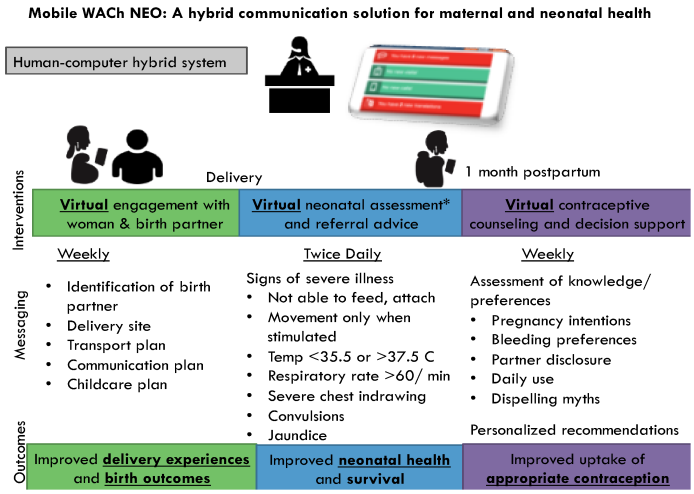

Figure 8: Components of the Mobile WACh NEO pilot

As a result of the findings from the original Mobile WACh RCT, and our interest in innovations to support neonatal survival, we initiated a pilot project, Mobile WACh NEO (Figure 8), with the Saving Lives at Birth consortium. We modified the Mobile WACh system and messaging approach to deliver messaging in late pregnancy and the first 2 months postpartum focused on providing tailored support by SMS in 3 strategic domains which have the greatest impact on maternal and neonatal health: *facility delivery planning, clinical assessment of neonates and the postpartum mother, and contraceptive decision support.* **We launched our pilot project in two high volume clinics in Kenya and have enrolled 800 women in 5 months, received thousands of SMS to date, triaged hundreds of concerns about maternal and neonatal health, and received timely reports of over 200 births and 20 adverse events.** Nurses and community health workers manage the messaging demand with 91% of women engaging with the messaging and sending on average 14 messages per woman to date, although most women are still in follow-up. We have noted several messages reporting depressive symptoms, and seeking assistance in practicing essential neonatal care and identifying infant illness. In exit interviews, women have almost unanimously requested continuation of the intervention. Although there is tremendous enthusiasm and demand for the intervention, and potential for impact, the pilot has no control arm and is not powered to determine clinical impact. **As a result, we propose to conduct a rigorous trial of Mobile WACh NEO to determine the effect of this two-way SMS intervention on neonatal mortality.** We will utilize paradata, process indicators, outcome data and exit interviews from the Mobile WACh NEO pilot to inform SMS message content development and approach.

Conceptual framework

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Figure 9 summarizes the conceptual framework that guides design and evaluation of the Mobile WACh NEO intervention. This framework is based on the Information-Motivation-Behavioral Skills (IMB) model of behavioral change, which posits that individual health behavior is predicted by the individual's access to information about the behavior, motivation, and behavioral skills to perform the behavior (67). Our overall hypothesis is that the Mobile WACh NEO intervention improves neonatal health through two complementary mechanisms. First, it provides mothers with *Information and Skills* through education, actionable SMS, instrumental support, and interactive triage to prevent, identify, and seek care for neonatal illness. Second, it provides mothers with *Motivation* though social and emotional support and psychoeducation to improve their mental health and self-efficacy, which in turn reinforces their ability to successfully implement protective essential neonatal care.

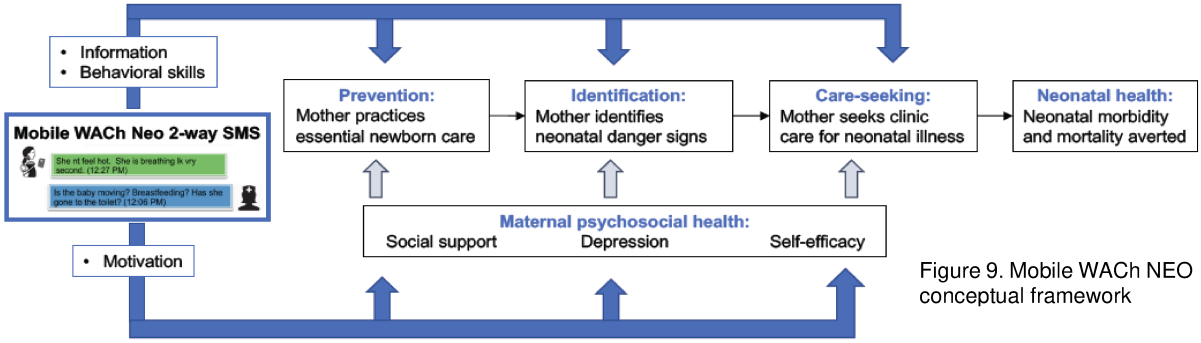

Figure 9. Mobile WACh NEO conceptual framework

8. RATIONALE

Despite recent achievements in reducing child mortality, neonatal deaths remain high, accounting for 46% of all deaths in children under 5 worldwide. Neonatal morality in Kenya is reported to be 22.6 per 1000 live births, ranking among the countries with the highest number of neonatal deaths. Addressing the high neonatal mortality demands efforts focused on getting proven interventions to at-risk neonates and their families. Bidirectional two-way SMS communication with a HCW presents a unique opportunity to connect mothers to a HCW, increase "real-time" identification of neonatal danger signs and guide appropriate care seeking. At the same time, this communication can provide support to women during the critical peripartum period, increase self-efficacy and social support, and contribute to decreasing depressive symptoms, which may further improve care seeking. SMS communication is designed to supplement, not to replace, in person health care delivery. We propose a randomized controlled trial (RCT) of a semi-automated, two-way SMS intervention, ***Mobile WACh NEO***, to determine its effect on neonatal mortality, implementation of ENC, identification of and appropriate care seeking for neonatal illness, and maternal mental health.

9. HYPOTHESIS & STUDY QUESTIONS:

Our overarching hypothesis is that Mobile WACh NEO, a theoretically grounded two-way SMS intervention that connects women with healthcare workers in the critical period surrounding delivery of their babies, will improve their knowledge, skills and motivation to prevent, identify and seek care for neonatal illness, leading to improved maternal and neonatal health.

10. OBJECTIVES

10.1 Broad Objectives

Our overarching aim is to determine the effect of Mobile WACh NEO SMS on neonatal mortality and understand the mechanisms by which this innovation impacts neonatal health. **We propose to determine the effect of** Mobile WACh NEO SMS **on neonatal mortality,** essential newborn care**, care seeking, and maternal mental health in the first 6 weeks postpartum, in a 2-armed randomized controlled trial (RCT),** comparing essential newborn care SMS versus no SMS control.

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10.2 Specific Objectives

Aim 1: To determine the effect of tailored, systematic two-way Mobile WACh NEO SMS on neonatal mortality.

Hypothesis: Women randomized to Mobile WACh NEO will have lower neonatal mortality than women randomized to control.

Aim 2: To determine the effect of Mobile WACh NEO SMS on maternal implementation of essential newborn care and care seeking behavior.

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

2b. To compare knowledge of infant danger signs and care seeking for neonatal illness among mothers randomized to Mobile WACh NEOv ersus control.

Hypothesis: Implementation of essential newborn care, knowledge of neonatal danger signs, and clinic attendance will be higher in mothers randomized to Mobile WACh NEO SMS than control.

Aim 3: To determine the effect of Mobile WACh NEOSMS on longitudinal maternal social support, self-efficacy and depression among mothers randomized to Mobile WACh NEOversus control.

Hypothesis: Maternal self-efficacy and social support will be higher and depression will be lower among women randomized to Mobile WACh NEO than control.

Exploratory aim: To determine associations between maternal mental health, implementation of essential newborn care, care seeking and SMS engagement.

11. METHODOLOGY

11.1 Study Design

The study is a non-blinded randomized controlled trial.

11.2 Study Area Description

Study sites: The proposed study will be conducted at 6 sites in Kenya: Mathare North City Health Centre, Riruta Health Centre, Rachuonyo County Hospital, Ahero sub-District Hospital, Bondo District Hospital and Kisumu County Hospital. Neonatal mortality in the Nairobi slum areas, Kisumu and Homa Bay counties is particularly high (4) so communities in these areas stand to benefit the most from the Mobile WACh NEO intervention. These facilities represent a mix of rural and urban facilities, all with sufficient patient volume to assure feasibility of recruitment. From our ongoing studies at these sites we estimate ~260 women attend ANC per month at each site.

Letters of cooperation will be submitted in a subsequent modification to this application.

11.3 Study Population

Table 2. Summary of proposed eligibility, procedures and outcomes for study aims

Population	N	Inclusion Criteria	Data Collection
RCT			

Pregnant women	5000	• Pregnant • 28-36 weeks gestation • Daily access to a mobile phone (own or shared) on the Safaricom network • Willing to receive SMS • Age ≥14 years • Able to read and respond to text messages in English, Kiswahili or Luo, or have someone in the household who can help • Plan to be in the area for at least five months postpartum	• Screening questionnaire • Enrolment and follow-up questionnaires • Content of SMS conversations with Mobile WACh system
Post-RCT IDIs			
Postpartum women	60	Intervention RCT participant	• IDI

Study populations for each of the aims are summarized in Table 2. Two study populations will be included in the study:

1. Pregnant women (Randomized controlled trial) (N=5000)
   Inclusion criteria:
   - Age ≥14
   - Pregnant
   - 28-36 weeks gestation
   - Daily access to a mobile phone on the Safaricom network
   - Able to read and respond to text messages in English, Kiswahili or Luo, or have someone in the household who can help
   - Plan to be in the area for at least five months postpartum

   Exclusion criteria:
   - Currently enrolled in another research study
   - Previous participant in the Mobile WACh NEO RCT (i.e. with a new pregnancy)

To enhance generalizability, literacy will not be required if women have access to a partner or family member whom she would be comfortable to have read her the messages. This approach was developed in consultation with mothers in Kenya, who felt that involving their partner was acceptable and may engage more support, and has been successfully implemented in our previous Mobile WACh studies.

2. Postpartum women (post-RCT IDIs) (N=60)
   A subset of intervention RCT participants will be invited to participate in IDIs after they complete the intervention to evaluate their experiences with the intervention.

11.4 Sample Size Determination

11.4.i. RCT

Table 4 summarizes detectable differences based on the expected outcomes, assuming α=0.0055 (Bonferroni-adjusted for 9 hypothesis tests) and sample size 5000 (2500 per arm). Expected outcomes are based on those observed in our previous work in Kenyan pregnant women (unpublished data) (58, 64) or other publications (68).

Indicator	Outcomes (control)	Outcomes (intervention)	Absolute difference	Relative difference
Neonatal mortality per 1000 births[1]	25.0 23.0	13.8 12.2	11.2 10.8	0.55 0.53

Table 3. Power and sample size ranges.	Minimum detectable difference

	20.0	10.0	10.0	0.50
Initiation of BF within 1h; EBF for 6 weeks[2]	90.0% 80.0%	93.0% 84.1%	3.0% 4.1%	1.03 1.05
Application of substances to cord; Bath within 24h[2]	40.0% 50.0%	45.3% 55.4%	5.3% 5.4%	1.13 1.11
Number of clinic visits in first 6 weeks[2]	0.5 1.0	0.6 1.1	0.1 0.1	1.22 1.11
Number of danger signs correctly named[2]	3.0 5.0	3.1 5.1	0.1 0.1	1.03 1.02
Maternal depression[2]	19.0%	14.6%	4.4%	0.77
Maternal social support score; Maternal self-efficacy score (max 4.0)[2]	2.5 3.5	2.6 3.6	0.1 0.1	1.04 1.03

[1]α=0.05,[2]Adjusted α=0.0055, β=0.8, 2-sided tests

11.4.ii. IDIs

Sample size for qualitative data collection was determined based on the number of interviews needed to achieve saturation of concepts. It is estimated that 60 interviews will be sufficient to achieve saturation.

11.5 Recruitment, Screening and Consent Procedures

11.5.i. RCT

Recruitment: Women will be recruited when attending routine ANC, through in-person outreach by study staff.

Screening and consent: Interested patients will be asked to provide verbal consent for screening (see screening consent script), consenting women will be asked screening questions to assess eligibility and, if eligible (see inclusion criteria above), be invited to participate in the study. Women willing to participate in the study will be asked to provide written informed consent form. The age of consent in Kenya is 18, but pregnant women age 14 or older are considered emancipated minors and can consent independently. Discussions between study staff and potential participants will be conducted in a private secluded place to maintain privacy.

11.5.ii. IDIs

Recruitment: Participants from the intervention arm will be classified into high, medium and low interactors based on their engagement or use of the Mobile WACh NEO program i.e. how often they send or respond to SMS. We will then randomly select 10 from each group to participate in interviews (IDIs). They will be invited to participate in IDIs while they are still on-study. We will also interview 30 women among those with neonatal complications or demises. Based on our previous studies we anticipate that half of the women who lose their babies want to remain connected to the program. We will select women for IDIs from among those who agree to remain connected to the program even after their loss.

11.6 Data Collection Procedures

11.6.i. RCT

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Intervention package: We propose to utilize Mobile WACh, a human-computer hybrid system used in our previous studies, which enables seamless two-way SMS communication and patient tracking, to provide consistent support to women and their infants during the peripartum period and 6 weeks into the baby's life. Women will receive automated theoretically grounded SMS messages targeting the appropriate peripartum period (Figure 10) and will have the capability to respond and spontaneously message a nurse based at the clinic. During pregnancy, automated SMS will be delivered weekly. Two weeks prior to the participant's estimated due date (EDD), daily messaging will begin, and will continue for two weeks after delivery is ascertained. If delivery is not confirmed by 43 weeks gestational age, the participant will be automatically moved to the postpartum messaging track. Thereafter, SMS will be delivered every other day for the remaining four weeks. Automated SMS will be delivered at times and in languages based on patient preferences. We have partnered with a local premium rate service provider (PRSP), Africa's Talking, to provide SMS dialogue free of charge to participants. Women who experience pregnancy or infant loss will be enrolled into an infant loss track where they will receive messages of support.

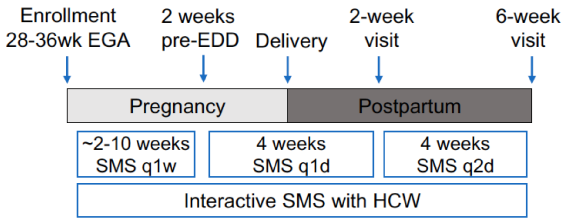
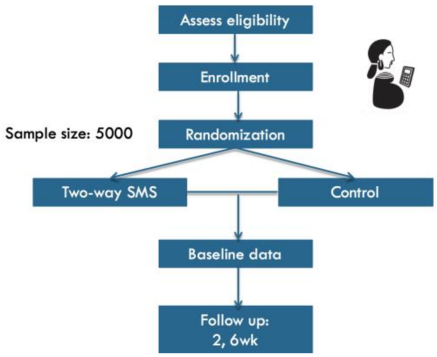


Figure 10. Mobile WACh NEO intervention

Randomization:



Participants will be randomized to 1) Interactive two-way SMS dialogue or 2) Control (no SMS), using 1:1 allocation. A randomization list will be generated by the study statistician using random block sizes in statistical software. Randomization will be stratified by site. This randomization list will be programmed into a computer program on an internet-based randomization platform. Each study site will be assigned unique user names and log in credentials for traceability purposes and ensuring that the randomization process is controlled.. Study staff will use their unique credentials to log in to the randomization program. The program will display the allocation after staff have entered the participant ID. The allocation will be recorded in the program for further traceability. The study arm will be unblinded to participants and study staff. The control arm will receive standard care and education provided in ANC by MCH clinic staff. Because the study aims to determine mHealth benefits in addition to routine clinical care, MNCH services will be delivered by the MOH programs with minimal clinic interactions with study personnel. The intervention will be delivered between 28 weeks of gestation and 6 weeks postpartum.

Data collection:

Participants will be followed from enrolment (28-36 weeks gestation) up to 18 weeks postpartum. All clinical care will be managed through the existing MCH infrastructure. The study visit schedule will be aligned to routine postpartum and infant visits: enrolment visit in pregnancy (28-36 weeks gestation), 2 weeks postpartum and 6 weeks postpartum. Active tracing will be performed through phone calls and home visits to maximize completeness of data at study visits. Participants who do not report their delivery by 40 weeks will be contacted by phone, followed by home tracing if not reached by phone. Further, participants who are 1 week late for their 2-week or 6-week postpartum visits will be traced by phone. Participants who are 1 week late for their 6-week visit and cannot be reached by phone will be traced at their home. Participants who do not wish to come to clinic for their 2-week or 6-week visit will be offered to complete their visits **by phone or at home** in locations that ensure participant safety and confidentiality. This approach has been successful and acceptable in our previous studies in this population (31, 64, 69). During the consent process, study staff will collect contact information and permission to contact a family member or trusted individual who they may contact in case of long-term lack of communication from the participant. This person may be contacted as part of active tracing.

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A tablet-based screening questionnaire will be used to assess eligibility and collect sociodemographic characteristics. Following enrolment in the RCT and randomization, a tablet-based enrolment questionnaire using an open-source tablet-based data collection system (Open Data Kit) will be used to collect enrolment data including: demographics, clinical and sexual history, family planning, experience with SMS and technology, social support, intimate partner violence, and depression.

At each visit, a standardized questionnaire will evaluate self-reported outcomes (Table 4), experience with the intervention (for intervention participants) and participant clinical characteristics that may be associated with the outcomes, such as delivery experience, maternal and child health status, breastfeeding, care-seeking, cord care, depression and social support. Between study visits, data will be abstracted from patient clinic records to ascertain clinical outcomes such as deliveries, clinic/hospital visits, and infant or maternal deaths (Table 4). The data will be abstracted from available facility records including MCH cards, facility registers (hospitalization, ANC, CWC, PNC), and EMR systems. The study nurses will review clinic records daily to check for deliveries and clinic visits from study participants. We have successfully employed this approach in a previous RCT, Mobile WACh-X (64). In addition to contributing to ascertainment of trial outcomes, abstraction of clinic records will enable personalization of messaging, for example initiating postpartum messaging after a participant delivers.

Medical extraction forms will be completed by data teams: delivery information, infant admissions, maternal health, infant health, maternal mortality, and infant mortality.

When the study team learns of an infant death through an SMS message, phone call or clinic record review, the study team will contact the participant to arrange a visit to conduct a verbal autopsy. Verbal autopsies will be performed about 6 weeks after the infant death, either in the clinic or at the participant's home based on their preference.

Participants will be provided Ksh. 400 per visit to compensate for time and transportation expenses to participate in the study. We will provide this monetary compensation to each participant at the conclusion of each study visit.

Data collection instruments

Data collection instruments will include forms to record data from participant surveys, to include:

- Demographics
- Clinical and sexual history
- FP use
- Experience with SMS and technology
- Intimate partner violence
- Depression
- Social support
- Delivery report
- Infant health
- Maternal health

11.6.ii. IDIs

IDIs will be performed in a private area within the facility. Participants will meet a trained interviewer who will ask questions and take notes. Consent will be obtained from participants to take notes and audio record the discussion. The interviewer will describe procedures and norms for discussion and participation. Participants will be given a chance to ask questions regarding procedures prior to the discussion. Their socio-demographic information will be documented in separate forms. Socio-demographic information that will be captured include: age, marital status, education level, employment, number of children.

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We will submit an IDI guide in a future modification.

Interviews will be conducted in English, Kiswahili, or Luo depending on participant preferences. Thereafter, notes will be compared to audio-recordings to fill in missing information and transcribed to English (if necessary). Transcribed data will be de-identified. Tape-recorded discussions will be destroyed no later than 3 years after conducting the IDI.

Participants will be provided refreshments and Ksh. 400 to compensate for time and transportation expenses to participate in the study. We will provide this monetary compensation to each participant at the conclusion of each interview.

11.7 Data Analysis

Table 4: RCT outcomes

Outcome	Role	Indicator	Source	Timing of ascertainment	Statistical Analysis
Aim 1					
Neonatal mortality	Primary outcome	Death during 1st 28 days of life	Questionnaire, clinic records; verbal autopsy	2 and 6 week visits, ongoing record abstraction	Cox proportiona hazards
Aim 2					
Initiation of early breastfeeding	Secondary outcome	Breastfeeding in 1st hour of life	Questionnaire	2 week visit	Poisson regression (robust standarc errors)
Exclusive breastfeeding	Secondary outcome	Cessation of EBF in 1st 6 weeks of life	Questionnaire	2 and 6 week visits	Cox proportiona hazards
Thermal care	Secondary outcome	Bath in 1st 24 hours of life	Questionnaire	2 week visit	Poisson regression (robust standarc errors)
Cord care	Secondary outcome	No application of substances to cord	Questionnaire	2 week visit	Poisson regression (robust standarc errors)
Maternal knowledge of neonatal danger signs	Secondary outcome	Number of the 7 danger signs or symptoms successfully named	Questionnaire	2 and 6 week visits	Poisson GEE
Appropriate care seeking	Secondary outcome	Number of clinic visits with danger sign and/ or hospital admissions reported in 1st 6 weeks	Questionnaire, clinic records	2 and 6 week visits, ongoing record abstraction	Poisson regression
Aim 3					
Depression	Secondary outcome	Score above diagnostic threshold (≥12) for Edinburgh Postnatal Depression Scale (70)	Questionnaire	Enrolment, 2 and 6 week visits	Poisson regression (robus standard errors)
Social support	Secondary outcome	Score using MOS Social Support Survey (71)	Questionnaire	Enrolment, 2 and 6 week visits	Linear GEE

Self-efficacy	Secondary outcome	Score using Self-efficacy in Infant Care Scale (68)	Questionnaire	Enrolment, 2 and 6 week visits	Linear GEE

For IDI analysis, two analysts will independently code transcripts to identify themes and sub-themes, coordinating analyses to create a comprehensive codebook and concept map. We will use domains identified under the IMB theory and our conceptual model to categorize participants' perceived intervention functions.

11.8 Study Materials

Equipment: The grant award includes support for SMS platform messaging delivery and receipt, 6 tablets, field office supplies (stationary, paper, toner), 6 laptop computers.

Personnel: The grant award includes support for KNH, UW and MOH investigators, clinic personnel, the data team, and two study coordinators (clinical coordinator (Nairobi based) and overall coordination (Seattle based)). Study personnel working in Kenya will be hired through KNH according to standard procedures.

11.9 Training Procedures

Dr. John Kinuthia, Dr. Jennifer Unger, Dr. Keshet Ronen, Daniel Matemo, Jenna Udren, Brenda Wandika and Peninah Kithao will supervise training of clinical personnel in study procedures. This will include research ethics, neonatal health and FP counselingand completion of surveys.

11.10 Quality Assurance Procedures

Clinical care: The study will adhere to Government of Kenya guidelines for the care of pregnant/postpartum women and their infants; however, no clinical care will be provided by study staff. Data collected as part of the study will be abstracted from the mother's "Mother & Child Health Booklet" or clinic medical records.

Adherence to protocol: Weekly reporting of enrolment, follow-up, medical complications and results will enable us to monitor that the study is running according to approved protocols. Frequent reporting will also enable us to quickly respond to any problems that arise during the study.

12. ETHICAL CONSIDERATIONS

12.1 Consent explanation

Please see the attached consent forms:
Consent 1: RCT study participation

12.2 Institutional Review Board

This is a collaborative research proposal that will involve field procedures in Nairobi and data analyses in Nairobi and Seattle. The study will be reviewed by the Kenyatta National Hospital/University of Nairobi (KNH/UON) Ethics and Research Committee (ERC), and the University of Washington Institutional Review Board (IRB). The study will not recruit subjects prior to approval from both the UW IRB and the KNH/UON ERC.

12.3 Risks to subjects

Physical: The study involves no medical interventions therefore we anticipate no risk of serious harm to participants.

Other: SMS: There is a potential risk of disclosure of an individual's person information to others in situations where phones are shared or stolen. We will minimize these risks through counseling in the informed consent process and ensuring women understand the type of messaging that will occur.

Access to clinical records: There could be a breach of confidentiality in the process of retrieving participants' medical records. This will be mitigated by training all study staff on data management and storage to ensure confidentiality of sensitive data is maintained.

Loss of Confidentiality in IDI: Women will be notified that by participating in the IDI, loss of confidentiality is a possible risk of participating. They will be informed that this is very unlikely as every measure will be taken to ensure confidentiality.

Alternative treatments or procedures: Not applicable

12.4 Protection against risks

Informed consent: Study staff will give potential participants verbal and written information about the study. Consent will be obtained and documented in verbal and written forms. Participants will have a chance to ask questions about the study, and offered participation. They will be enrolled in the study after providing written informed consent. Mothers will provide informed consent for study participation on behalf of their infants.

SMS: There is a potential risk of disclosure of an individual's person information to others in situations where phones are shared or stolen. However, we will not send any sensitive information via text. Study staff will specifically demonstrate example messages, to ensure potential cohort study participants agree to receipt of this information. Participants will only be enrolled once they understand study procedures and find the messaging acceptable.

Access to clinical records: There is could be a breach of confidentiality in the process of retrieving participants' medical records. This will be mitigated by training all study staff on data management and storage to ensure confidentiality of sensitive data is maintained. Databases will not include patient identifiers and will be encrypted and password protected.

Loss of confidentiality in IDI: We will assure women of protection of confidentiality.

DSMB: Clinical care will continue to be provided as prescribed. As this is a clinical trial, we will have a DSMB who will regularly monitor protocols and outcomes.

Undiagnosed conditions: It is possible we will detect previously undiagnosed conditions such as depression and intimate partner violence. Participants will be referred for appropriate health and social services.

SMS withdrawal: Participants in the intervention group may withdraw from receiving SMS messages at any time. Study staff will complete an SMS Withdrawal form for any participants who wish to withdraw from the system. Participants who withdraw from SMS can continue or withdraw from the study.

Study withdrawal: Participants may withdraw from the study at any time for any reason. Study staff will complete a Study Termination form for any participants choosing to termnate early. All data collection and SMS messaging will discontinue at that point.

12.5 Potential benefits

The study will contribute to our understanding of how to deliver education and counseling to help women and families. It will also provide information that can be used to improve services to ensure more women attend clinic visits, get help with their delivery, and are provided with family planning options. It may help get more babies immunized. The study will also shape future SMS programs. Participants in the intervention arm may personally benefit from having access to advice about infant heath and infant illness. It may lead to improved care of the infants, better identification of infant illness and more appropriate care-seeking.

12.6 Compensation

A nominal travel reimbursement will be provided for participant travel to the study clinic (see section 11.6).

12.7 Importance of the knowledge to be gained

This study will determine the efficacy of 2-way communication to improve neonatal and maternal postpartum outcomes.

13. DATA MANAGEMENT

IDIs

IDI audio recordings and transcripts will be uploaded to a password-protected computer and erased from the recorder within one day of interview. Recordings will be erased once transcripts have been validated, no more than 6 months after generation of the recording.

Questionnaires

All questionnaires will be administered using the tablet-based ODK platform. Tablets will be password-protected and questionnaires will be transmitted to a secure server daily and erased from the tablets. Data will be transmitted via secure socket layer (SSL) and only accessible by authenticated users. Tablets will be stored in a secure, locked office accessible to study staff only. All participants will be assigned a non-identifiable study ID number upon enrolment. All data records will be identified by study ID only. The link between identifiable participant information and study IDs will be locked in a secure, locked location and destroyed following study completion. Study analysts will receive only coded data.

Paper records

Consent forms and participant locator information will be stored in paper forms. These will be stored in a secure, locked location and destroyed following study completion.

Data Ownership

The proposed project is a collaborative effort between investigators at the UW and KNH. The aforementioned institutions will jointly share ownership of the data. Study investigators at the UW and KNH will have full access to the data. Authorship on publications, conference presentations, abstracts and other materials generated from this study will reflect contribution to design, execution and analysis of the study.

Data Release/Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

14. RESULTS DISSEMINATION

We will establish 4 community advisory boards, one for each facility. This will include medical providers and community members living in the area. We will disseminate results to this board twice a year and ask for guidance if community issues arise.

Study findings will be shared with the participating facilities and Kenyan Ministry of Health at its conclusion as a presentation or written report. Findings will be disseminated to the research community in the form of conference presentations and journal articles.

15. STUDY LIMITATIONS

SMS alone cannot directly improve the health care system or address the third delay in care (delay in receiving quality care). There are many other external factors – partner, socioeconomic factors, quality of facility-based care – that may not be modulated by SMS messaging. This may limit our ability to detect an impact on the primary outcome of neonatal mortality. Evaluation of the impact of SMS on secondary outcomes of ENC, knowledge of warning signs, care seeking and maternal mental health will nonetheless enable us to assess whether the SMS intervention has the desired impact and has potential to improve mortality in combination with additional health systems strengthening. Moreover, these **secondary outcomes have value in improving neonatal and maternal health in their own right.** Fidelity and generalizability of dialogue interventions are challenging. We have extensive experience in standardizing messaging dialogue, but it will not be possible to completely standardize the nurse responses in the intervention. This challenge however is part of routine medical care and any type of behavioral interventions involving health workers. Implementation and evaluation in four sites will increase the generalizability of any measured effect. With regards to the care seeking outcome, babies in the control arm may have higher numbers of clinic visits and/ or hospitalizations if their mothers are less likely to practice ENC or if mothers seek care later in the illness process. If we observe this effect we will compare illness severity at presentation between the two arms using a validated neonatal illness assessment. Women in the trial cannot be blinded to their assignment, which may lead to performance bias. Additionally, outcomes obtained by self-report could introduce bias for social desirability, but this will likely occur across all arms.

16. STUDY TIMELINE

The study timeline is summarized in Figure 11. We anticipate that this study will take 5 years to complete. In the first year, we will obtain ethical approval from institutional review boards at the University of Washington and Kenyatta National Hospital. During this time, we will develop and refine study tools and finalize standard operating procedures and publish the clinical trial protocol. We will also adapt the messaging platform technology based on final pilot project data and finalize the message bank for the intervention. Following IRB approval, field site preparation will take 3 months, including hiring and training of site staff, and conducting of mock enrolments and messaging. We will also conduct community sensitization and outreach to ensure the community is aware of the purpose of the project. We will recruit and enroll participants and conduct follow-up over a 24-month period. The last follow-up visit will occur in quarter 1 of year 4. We will conduct the post RCT interviews in Year 4. Approximately 6 additional months will be needed for data verification and cleaning, ascertainment and transcription of any outstanding clinical records. Data analysis and dissemination including manuscript submissions will occur in Years 4-5.

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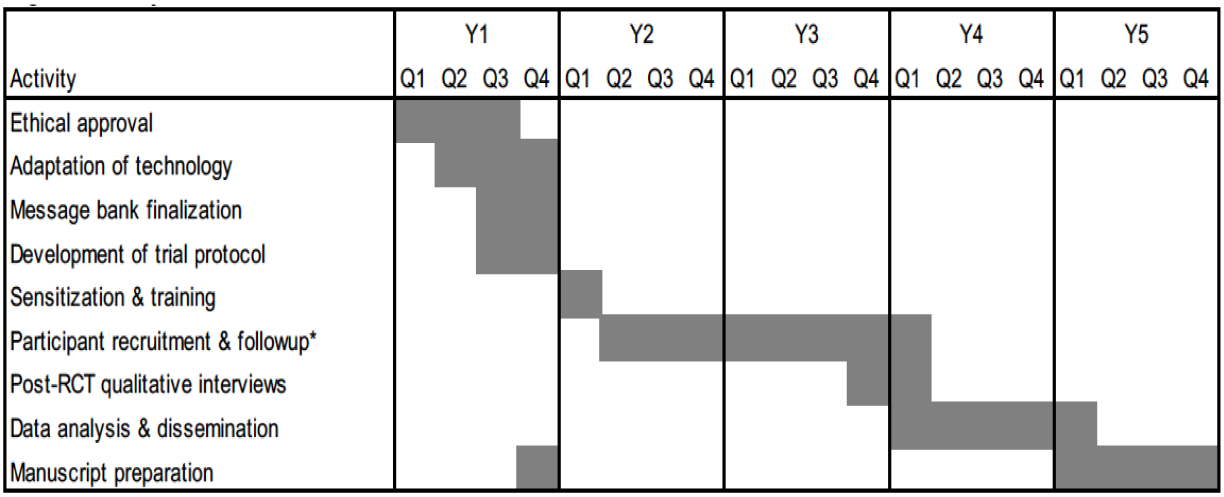
Figure 11. Study timeline



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STUDY PROTOCOL

V2.2 October 5, 2020

APPENDIX I COVID-19 RESPONSE PROCEDURES

In response to the COVID-19 pandemic and policy changes issued by the Kenyan Ministry of Health (MOH), we are ensuring study procedures protect the health and safety of study participants and staff. Study visits align with routine patient clinical care schedules, and all participants and staff will follow MOH guidelines within the facility to reduce risks of potential exposure i.e. use of personal protective equipment, appropriate distancing with participants, reducing contact with commonly touched surfaces, handwashing and environmental cleaning. We will provide participant reimbursement via M-PESA to minimize tough points between staff and participants. All data will be collected by study staff on tablets to which only they will have access and will follow disinfection procedures. Participants will not be required to touch any study materials.

Revisions to Data Collection Procedures

Any in-person home visits for follow-up or infant verbal autopsy, or clinic visits for in-depth interviews will be suspended until social distancing measures have been rescinded by the Kenyan government. Follow-up data collection will occur via study visits aligned only with routine clinical care or phone as already noted in this protocol. Verbal autopsies and in-depth interviews will be conducted via phone until in-person study-specific visits are approved by appropriate authorities.