Developing Low-Cost Universal Malnutrition Screening for Low Income Countries – the MAMMS Trial

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1. Title of the Project

Developing Low-Cost Universal Malnutrition Screening for Low Income Countries – the MAMMS Trial

2. Investigators and Institutional Affiliations

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3. Lay Summary

What is the problem?

Malnutrition contributes to 45% of childhood deaths in low and middle-income countries, but current nutritional screening strategies fail to identify the majority of children with malnutrition and they are very expensive.

What question are we trying to answer?

We aim to test if mothers can measure their child's nutritional status with support from study staff via a text-message (SMS) based platform.

Where is the study taking place?

Migori and Homa Bay counties: Migori County Referral Hospital, St. Joseph's Mission Hospital, Rongo, Awendo, Kuria-west (Isebania), Nyatike (Macalder) Sub-County Hospitals, Macalder Mission Dispensary,
Homa Bay County Referral, Makongeni Sub-County, and St. Paul Mission Hospitals.

How many people does it involve and how are they selected?

The study aims to recruit 1,315 mother-infant pairs attending maternal and child health (MCH) clinic (or a community outreach day for the MCH clinic) for an immunization, weight check, or an acute illness visit. Each mother-child pair will be randomly selected to either the MAMMS intervention or standard of care (SOC) and followed for 180 days. Mothers who do not have access to a mobile phone or do not plan to remain in the catchment area for more than 180 days will be excluded.

What does the study involve for those who are in it?

After enrolment, study staff will counsel mothers on nutrition and show mothers how to assess nutritional status using a tape measure called a mid-upper arm circumference (MUAC) tape. Study staff will collect social information, and data on maternal and infant health from all participants. Mothers in the MAMMS arm will send their child's nutritional measurements to our staff each week using a 2-way text message program. Mothers in the SOC arm and the MAMMS arm will be asked to return to clinic for a day 180 follow up visit which will include and child health check, anthropometry measurements, and feeding assessment as well as maternal anthropometry.

What are the benefits and risks/ costs of the study for those involved?

Mothers will benefit from a short counselling session about child nutrition. Children who develop malnutrition will receive standard treatment per Kenya guidelines. All children will receive a free child health check at day 180 follow up visit. Risks include potential loss of confidentiality, but all necessary steps will be taken to ensure data remains secure and confidential. Travel costs and time associated with participation will be reimbursed at each scheduled visit.

How will the study benefit society?

The communities in this study have a high prevalence of undernutrition. Findings from the MAMMS trial are expected to lead to improvements in the diagnosis of childhood malnutrition.

When does the study start and finish?

Participant recruitment will begin following receipt of ethical approvals and be completed within a 24-month period.

4. Abstract

Acute malnutrition affects 52 million children, costs $2.1 trillion globally, and contributes to 45% of deaths among children under five years of age. Affordable home-based treatments can prevent many of these deaths, with success rates >97.5% if malnutrition is identified early. If identified late, treatment failure rates increase to 16%. Malnutrition programs currently rely on community health volunteers to screen children, which can lead to high costs, low screening coverage, and late identification.

MUAC is the preferred community malnutrition screening tool. Evidence has shown that mothers can accurately measure their child's MUAC and identify malnutrition. Yet, there is no method of linking these mothers to the nutritional care that malnourished children require. Training mothers to use MUAC tapes to monitor their child's nutritional status through a short message service (SMS) mobile health system could increase screening coverage and facilitate rapid engagement with nutritional services where necessary.

We propose to test the "Maternal Administered Malnutrition Monitoring System" (MAMMS) in a randomized controlled trial in Kenya. Mothers will be taught to measure their child's MUAC at 6 or 9-month immunization, weight, acute illnesses at the MCH, during MCH community out-reach and during 6-month follow up they will receive a weekly SMS prompting them to measure and

send their child's MUAC to a computer system which will alert a health worker when a child with malnutrition is identified. This scalable system could enable nutrition programs to optimize screening coverage, leading to early identification of malnutrition, lower costs and a reduction in under-five mortality.
Recruitment is anticipated to take 2 years following receipt of ethical approvals from the University of Washington and Kenya Medical Research Institute. Data will be managed in accordance with Good Clinical Practice and Health Insurance Portability and Accountability Act requirements. Results will be shared with the clinic and community at local and international meetings. The primary manuscripts will be published within 2-years of study completion.

5. Abbreviations

ALIMA	Alliance of International Medical Action
ART	Antiretroviral Therapy
CAB	Community Advisory Board
CCC	Comprehensive Care Clinic
CMAM	Community Management of Acute Malnutrition
CRF	Case Report Form
DALY	Disability-Adjusted Life Years
DSMB	Data Safety and Monitoring Board
FGD	Focus Group Discussion
GCP	Good Clinical Practice
KEMRI	Kenya Medical Research Institute
MAM	Moderate Acute Malnutrition
MAMMS	Maternal Administered Malnutrition Monitoring System
MCH	Maternal Child Health
mHealth	Mobile Health
MUAC	Mid-Upper Arm Circumference
PCR	Polymerase Chain Reaction
RCT	Randomized Controlled Trial
RUSF	Ready-to-use Supplementary Food
RUTF	Ready-to-use Therapeutic Food
SAM	Severe Acute Malnutrition
SOC	Standard of Care
SOP	Standard Operating Procedures
SMS	Short Message Service
TOT	Training of Trainers
UW	University of Washington
WACh	Center for Women, Adolescent and Child Health
WHO	World Health Organization
WLZ	Weight-for-length Z-score

6. Background

Acute malnutrition is a critical driver of paediatric mortality that must be addressed to achieve global child health targets.[1–4] Over 52 million children become malnourished each year, costing the global economy an estimated $2.1 trillion and contributing to an estimated 45% of all child deaths.[1,5] Provision of ready-to-use therapeutic foods (RUTF) and nutritional counselling in the community is a highly effective method of preventing deaths among malnourished children.[6–10] However, UNICEF estimates that only 17% of malnourished children receive treatment.[11] Among children who are treated, the diagnosis of acute malnutrition is often made late in their disease when the risk of complications and death increases from 2.5% to 16%.[11–13] Increasing the coverage and frequency of nutritional screening to identify malnourished children earlier in the disease process is a critical step toward achieving global child health goals.

Community Based Management of Acute Malnutrition (CMAM) programs rely on active and passive case identification.[11,14,15] During active identification, community health volunteers conduct house-to-house or community centre based mass screening of children aged 6-59 months using MUAC, an easily administered and widely implemented tool for community nutritional screening. Active case identification has proven moderately successful in humanitarian and development settings. However, its reliance on community health volunteers requires substantial human resource investment, which raises program costs and often systematically omits vulnerable populations, such as families living far from the treatment center or families with two working parents.[15] Consequently, it is recommended that active case identification be utilized during initial program implementation to sensitize communities, and that passive identification be the mainstay of mature nutritional programs.[14] Passive identification relies on training of healthcare professionals and community leaders to identify malnutrition when children present to healthcare facilities or community center. Unfortunately, most children present to these facilities because they have developed medical complications, which are associated with a 6-fold increase in the case fatality of acute malnutrition. Despite significant investment in CMAM programs, UNICEF spends between $120-165 million per year supporting CMAM programs with Ministries of Health and other funders often matching or exceeding these contributions,[15–17] the limitations of active and passive case identification severely constrain coverage. Due to the cost and complexity of delivery, a recent meta-analysis of CMAM programs in 21 countries found that only 38% of malnourished children who live within the target population of a CMAM program are identified and treated.[18]

Given the high burden of morbidity and mortality associated with childhood malnutrition, CMAM programs are often considered cost-effective.[15,19] However, the financial and human resource investments required to implement active and passive case identification are high and often unsustainable, particularly considering the low coverage and missed cases.[11,19–24] Typical CMAM programs cost between $100 to $500 per child treated.[25,26] In contrast, mass deworming programs cost $0.50 per person treated and the complete Expanded Program on Immunization Schedule costs $18 per child fully immunized.[27,28] These high costs deter many countries from implementing CMAM programs.[15] Of the 50 countries that implement routine CMAM programs, all are heavily dependent on external funding.[15] A recent analysis by the International Rescue Committee demonstrated that increasing malnutrition screening coverage was the most effective method of lowering the cost per child treated.[25] A novel high coverage screening platform, combined with ongoing efforts to reduce the price of commercial RUTF, could make universal malnutrition treatment both achievable and affordable.

Task shifting MUAC assessment to a child's mother could increase screening coverage and allow field workers to focus on treatment rather than identification of malnourished children. Two studies and programmatic evidence from Niger have shown that mothers can use MUAC effectively, and that this leads to earlier identification of malnutrition in comparison to active and passive screening.[29,30] However, developing a generalizable strategy to deliver maternal MUAC training and provide support to mothers while their child is most vulnerable, remains a challenge. The six and nine-month child immunization visits, at which vitamin A and measles vaccines are provided, provide a strategic platform for maternal MUAC training. These immunization visits are well timed relative to malnutrition associated mortality, as the majority of malnutrition occurs between 6 months and 5 years of age, with the introduction of complementary feeds making children aged between 6-18 months particularly vulnerable.[31–33] Globally, 85% of children receive a 9-month vaccination, suggesting that grounding the MAMMS program in this platform could substantially boost nutrition program coverage.[34]

mHealth platforms capitalize on the proliferation of mobile phone coverage across low-resource settings and create efficient and reliable connections between families and health care providers.

MHealth interventions have demonstrated effectiveness across a wide range of health issues and health services, including increasing follow up clinic attendance and health relevant knowledge.[35] The University of Washington (UW), led by Dr. Jennifer Unger, has developed a hybrid computer-human SMS communication platform specifically designed to link Kenyan mothers to health care professionals in an effort to promote healthy maternal and infant behaviors.[38-41] Mobile WACh's platform and messaging have been used as a strategy to support patients in accessing proven interventions such as facility delivery, exclusive breastfeeding, family planning, antiretroviral therapy (ART), pre-exposure prophylaxis (PrEP), early identification of neonatal and infant illnesses and peripartum depression care.[36-39] Development of Mobile WACh over the last 5 years has progressed through careful qualitative work with end users, clinical pilot studies, and randomized trials. The Mobile WACH platform recently demonstrated that 2-SMS interventions can significantly decrease early weaning and increase postpartum contraceptive use. Mobile WACH provides an ideal system to enable routine maternal assessment of their child's MUAC, and deliver prompt nutritional management when indicated (Figure 1).

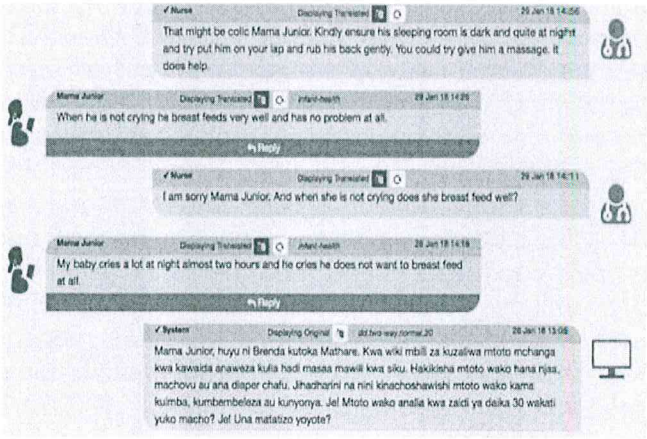


Figure 1: Exert from a SMS exchange between a participant and study nurse via the Mobile WACh

Kenya has an endemic level of moderate acute malnutrition (MAM, approximately 4% have weight-for-height z-score <-2 z-scores) among children under five years of age, with Migori and Homa Bay counties having an estimated MAM prevalence of 2%.[40] This region also suffers from recurring droughts and frequent famines. Thus, while the prevalence of childhood MAM is estimated to be lower in Migori and Homa Bay counties, this may be due to lower screening coverage and identification of childhood MAM and we may anticipate the prevalence of MAM to be comparable to the 4% observed in other regions of Kenya. Kenya's CMAM program, launched in 2008, has made significant progress in helping children recover from malnutrition. It has treatment success rate of 80.7% for SAM, 80.5% for MAM, and 84.6% for children admitted to hospital with SAM.[41] The Kenyan CMAM program has a strong policy framework and meets the international standard for recovery rates among children enrolled in CMAM programs, but the geographic coverage (number of facilities connected to a CMAM program) in Kenya is only 33%, and is as low as 16% in population dense counties such as Nairobi.[41] Treatment coverage, defined as the percent of malnourished children receiving treatment, is unknown, and evidence from UNICEF's national monitoring demonstrates that large sections of slum and rural settings are systematically missed even when they fall within an existing CMAM target area. The primary constraint to increasing CMAM services are program costs, the low population density of some rural areas and extremely high population density of urban slums. Kenya has become a leader of mHealth interventions with 93% of Kenyan households owning a mobile phone.[42] Collectively, these data suggest that Kenya is an ideal and generalizable testing environment for mHealth interventions designed to support nutrition programs.

While CMAM programs are a highly effective method of preventing deaths among malnourished children,[51-53] they require an intensive regimen of caregiver education, daily administration of RUTF and antibiotics and regular clinic visits over 6-16 weeks. In 95% of cases,[54] the child's mother delivers this care and her ability to engage in the CMAM regimen is a critical

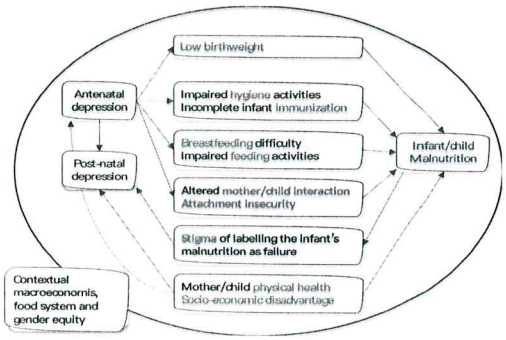


Figure 2: Conceptual model of maternal depression's links to childhood malnutrition,

factor in the recovery of the child (Figure 2). Among 244 mothers with children admitted to an inpatient malnutrition ward in Malawi, 71% had clinically significant symptoms of depression,[55] but it is unclear if CMAM treatment programs have a similarly high prevalence of depressive symptoms. Maternal depression is associated with decreased self-efficacy, poor motivation, and diminished ability to meet the child's needs, which may reduce a mother's ability to implement at home medical treatments during a child's illness.[56,57] Maternal antenatal and postpartum depression have also been associated with adverse infant outcomes including undernutrition, diarrheal diseases,[53] and infant hospitalization and death.[58,59] CMAM programs ask mothers to engage in an intensive treatment regimen for their malnourished child at a time when the burden of depression is likely to be a barrier to successful treatment implementation.
We propose an intervention called the "Maternal Administered Malnutrition Monitoring System (MAMMS)", in which mothers attending 6-month and 9-month infant immunizations in Kenya will be trained to measure and send their child's MUAC each week using a 2-way SMS communication program designed to support identification, follow up and treatment of acutely malnourished children. These weekly MUAC measurements creates an opportunity to evaluate the implications of transitioning from a malnutrition definition based on a single MUAC assessment at one time point (i.e. MUAC <12.5cm) to a longitudinal MUAC trajectory-based definition (e.g. decrease in MUAC >0.4cm per week). In low-resource settings, growth faltering is defined by single growth measurements as longitudinal measurements are typically not feasible. The MAMMS system may allow providers to identify children before they become malnourished rather than waiting for the child to cross into a high-risk nutritional state. This study also provides an opportunity for deeper understanding of the prevalence of depression among mothers with a child in a CMAM treatment program and the impact of maternal depression on their child's nutritional recovery. Increased screening coverage and early identification of childhood acute malnutrition through the MAMMS platform could facilitate reductions in malnutrition-associated mortality and reduce the cost per child treated for national nutrition programs.

7. Justification for the Study

Acute malnutrition affects 52 million children, costs the global economy $2.1 trillion, and contributes to 45% of deaths among children under five years of age annually.[1,5] Affordable home-based treatments can prevent many of these deaths, with treatment success rates above 97.5% if malnutrition is identified early (i.e. within the first month of malnutrition developing).[6–10] If identified late, treatment failure rates increase, and mortality can reach up to 16%.[11–13] Malnutrition programs currently rely on community health volunteers to screen children, which can lead to high costs, low screening coverage, and late identification. An analysis of malnutrition treatment programs in 21 countries observed that only 38% of the target population was screened at an average cost of $300 per child treated.[18] Current screening strategies fail to identify children with malnutrition and provide them cost-effective treatment. MAMMS may be a scalable childhood growth monitoring system that could enable nutrition programs in low and middle- income countries to optimize screening coverage, leading to early identification of malnutrition, lower costs and a reduction in global under-five mortality.

8. Null Hypothesis

The MAMMS intervention is not associated with i) early identification and treatment of acute malnutrition in young children; ii) accurate MUAC assessment between mothers and community health volunteers; iii) lower cost-per-malnutrition case identified.

9. Primary and Secondary Objectives

To test MAMMS in a randomized controlled trial in western Kenya, we aim to:

Aim 1: Determine if MAMMS leads to earlier identification and recovery from acute malnutrition.

Hypothesis 1.1: Children randomized to MAMMS who develop acute malnutrition (defined as

MUAC <12.5 cm) will be identified earlier in study follow-up than children in the control arm.
Hypothesis 1.2: Children randomized to MAMMS who develop acute malnutrition will be more likely to successfully complete nutritional rehabilitation (defined as no death, no hospitalization, no severe acute malnutrition, and resolution of moderate malnutrition within 4 months of diagnosis) than children in the control arm diagnosed with acute malnutrition.

Aim 2: Demonstrate the accuracy of maternal administered MUAC assessments compared to trained community health worker, and the ability of repeated maternal administered MUAC measurements to monitor early childhood growth.

Hypothesis 2.1: Maternally measured MUAC will be strongly correlated with health worker measured MUAC at baseline and during follow up. Hypothesis 2.2: A highly sensitive and specific growth trajectory that predicts moderate acute malnutrition can be identified using maternally measured MUAC.
Aim 3: Evaluate a) the acceptability, feasibility, fidelity and b) the cost per-child-treated of MAMMS relative to standard-of-care nutrition programs.

Hypothesis 3.1: MAMMS will be acceptable and feasible to mothers and health volunteers.

Hypothesis 3.2: MAMMS will have a substantially lower cost-per-malnutrition case identified and higher cost-effectiveness than standard screening approaches.

Aim 4: Determine the relationship between maternal sociodemographic and health characteristics and childhood acute malnutrition.

Hypothesis 4.1: Mothers with less social support, depression and lower socioeconomic status will be more likely to have children with acute malnutrition.

Secondary Objective:

Aim 5: We will determine the prevalence of maternal depressive symptoms at enrolment of their child in a CMAM treatment program and the association between maternal depression and attendance at routine CMAM visits and child nutrition outcomes.

Hypothesis 5.1: Mothers of a malnourished child enrolled in a CMAM treatment program will have a higher prevalence of depressive symptoms [based on Patient Health Questionnaire–9 (PHQ-9) scores] compared to age-matched mothers whose child is not malnourished.

Hypothesis 5.2: Mothers with higher PHQ-9 scores will retain less nutrition information delivered in CMAM programs and their children will be more likely to miss routine CMAM visits and will have longer treatment duration than children of mothers with lower PHQ-9 scores.

10. Study Design

Randomized Controlled Trial (RCT)

11. Study Sites

The MAMMS study will recruit and follow up mother-infant pairs attending maternal child heath (MCH) clinic or MCH community outreach day at Migori County Referral Hospital, St. Joseph's Mission Hospital, Rongo, Awendo, Kuria-west (Isebania), Nyatike (Macalder) Sub-County Hospitals, Macalder Mission Dispensary.
Homa Bay County Referral, Makongeni Sub-County, and St. Paul Mission Hospitals.

12. Study Population

The MAMMS trial aims to recruit 1,315 mother-infant pairs attending MCH clinic or MCH community outreach day and at risk of malnutrition (MUAC between 12.5-14.0 cm). After informed consent and completion of enrollment procedures, each mother-child pair will be randomized to MAMMS or standard of care (SOC) at a 1:1 ratio (in blocks of 10).

Criteria for inclusion of mother-infant pairs

- Infant aged between 5 months and 14 days – 12 months and 14 days with a MUAC of 12.5-14.0cm
- Access to a Safaricom mobile phone and can provide a mobile phone number
- Planning to remain in the catchment area >6 months and willing to return for 6-month follow up visit
- Mother is willing to be randomized to weekly SMS, measure and send weekly infant MUAC via SMS
- Able to read or write or has someone to help them read or write
- Willing and able to provide informed consent
- Attending MCH clinic (or an outreach day for the MCH clinic) for month 6 or 9 immunization, weight check or an acute illness visit.

Criteria for exclusion of mother-infant pairs

- Infant is younger than 5 months and 14 days or older than 12 months and 14 days of age.
- Infant is currently on treatment for malnutrition
- Inability to provide a safaricom mobile phone number
- Mothers that could not read or write and did not have someone to help them read or write
- Does not plan to reside in the catchment area >6 months
- Previously enrolled in this study
- Sibling currently or previously enrolled in the MAMMS Trial
- Infant enrolled in a clinical trial/research study with intervention to malnutrition treatment.

13. Sampling

Sample size determination

Based on documented immunization records across sites, we anticipate 133 children to attend 6-month and 301 to attend 9-month immunizations per month. Thus, we expect to enroll approximately 40 children per month across the study sites to reach the target enrollment of 1,315 children in 12-14 months. Mother-infant pairs will be randomized to MAMMS or SOC at a 1:1 ratio (in blocks of 10) following enrollment. We anticipate an equal number of male and female children to be recruited.

Power for each aim was calculated with Open Epi online software using the following formulae:

$$n_1 = \frac{(Z_{\frac{u}{2}} + Z_{1-p})^2 \bar{p}\bar{q}(r+1)}{r(p_1 - p_2)}$$

And

$$n_2 = rn_1$$

Where:

n_1= Number exposed; n_2= Number unexposed;

$Z_{\frac{u}{2}}$ = Standard normal distribution for two tailed test based on alpha =0.05

Z_{1-p} = Standard normal distribution for one tailed test based on beta level

r = Ration of exposed to unexposed

p_1 = proportion of exposed with disease, $q_1 = 1-p_1$

p_2 = proportion of unexposed with disease $q_2 = 1-p_2$

$\bar{p} = (p_1 + rp_2)/(r+1)$, and $\bar{q} = 1-\bar{p}$

Power Aim 1: The total sample size was calculated for the primary endpoint of increased ability to identify malnutrition (MUAC <12.5 cm) between randomization arms, assuming 80% power

and an alpha of 0.05 (see above formulae). We require 553 children in each arm (1,106 total) to detect a 2-fold increase in earlier identification of malnutrition between MAMMS and SOC arms, with a cumulative incidence of 4% acute malnutrition in children in Migori County as representative of underlying incidence in the SOC arm.[40] The incidence rate is based on prevalence to incidence conversion formulas, and assumes that we will identify 50% of children with acute malnutrition in the SOC arm. Thus, while the true incidence of acute malnutrition will be 8%, the incidence of acute malnutrition detected in the SOC arm will be 4%. To account for loss to follow up, we will recruit an additional 47 per group (94 total) for a total planned enrollment of 600 per arm (1,200 total). Children who develop malnutrition will be followed for an additional 4 months from diagnosis of acute malnutrition and recovery rates will be compared between randomization arms. Assuming 4% (n=24) malnutrition in SOC and 8% (n=48) malnutrition in MAMMS, and utilizing a time-to-event analysis, we will have 80% power to detect a 43% increase or decrease in recovery.

Between March and December 2020, research activities were halted due to the COVID-19 pandemic. This impacted 115 enrolled children that were in active follow-up. Study staff were able to remotely monitor the MAMMS system (intervention arm), but no home visits were conducted in the standard of care (SOC) arm and neither MAMMS nor SOC arms were able to complete the final 6-month study outcome visit. This has led to differential outcome ascertainment between the study arms as a higher proportion of children in the SOC arm have no known outcome after enrollment, while the MAMMS arm continued to receive weekly SMS messages and study staff continued to review the SMS messages. The DSMB and study statistician have recommended that we recruit replacement participants for these 115 children to remove the differential censoring caused by the COVID-19 pause and to ensure we have enrolled 1,200 children with possibility of 6-month outcome data to maintain original study power to evaluate our primary outcome above.

Power Aim 2: With a sample size of 553 in the MAMMS arm (accounting for attrition) at 2 time points, and conservatively assuming a weak correlation of r=0.35 between maternal and field worker MUAC measures, we will have 80% power at an alpha=0.05 to detect a 0.10 difference in correlation using a Fisher's z test. Assuming a moderate correlation of r=0.60, we will have at least 80% power to detect a 0.071 difference in correlation between maternal and field worker MUAC measures. Due to exploratory nature of the phenotypic MUAC trajectories to predict acute malnutrition, we do not have preliminary data for a sample size calculation.

Power Aim 3. The sample size for the qualitative data collection is based on the ability to reach data saturation by the re-emergence of key themes across data sources, time and resources. If during qualitative data collection, we are not able to reach data saturation using the pre-specified sample sizes for focus groups and individual interviews as detailed above, an additional four focus groups and three individual interviews will be conducted to ensure comprehensiveness and representativeness of the qualitative data.

The sample size for the cost effectiveness study is based on sample size calculation methods developed for Aim 1. We will use an incremental cost effectiveness ratio to determine the ratio of change in costs to the change in effects. In this study, the term "fidelity" reflects consistent and per protocol delivery of essential components of the intervention and their associated process outcomes. It is important to track intervention fidelity to ensure that the intervention is scalable in Kenya and feasible to replicate across other geographic settings. In this study, intervention fidelity is defined according to three categories (1) treatment delivery, (2) treatment receipt, and (3) technology acceptance. Fidelity to treatment delivery will be measured as the proportion of messages that are successfully delivered to a participant's mobile phone (based on automated tracking) and the proportion that are opened. Fidelity to treatment receipt will be measured as the proportion of delivered messages that are responded to as well as average monthly changes in

responsiveness over time (i.e. attenuation). Fidelity to technology acceptance will be measured as the proportion of caregivers who come to health facilities when messaged to do so as well as the proportion of mothers who report a continued interest in participating in the MAMMS intervention during end-line acceptability assessments. All measures of fidelity will be stratified by mobile phone ownership and maternal literacy.

Power Aim 4. The sample size for this aim is determined by the ability to detect an association between the lowest wealth quintile and developing acute malnutrition. Assuming 80% power, alpha=0.05, and a 7% risk of acute malnutrition among mother-infant dyads in the higher wealth quintiles, 564 children would be required to detect a 2.5-fold increased risk of acute malnutrition in the lowest quintile compared to the higher wealth quintile. Assuming the MAMMS intervention is successful, this sample size will allow the analysis to be conducted among the SOC arm. We will gain additional power if we compare the change in childhood MUAC measurements throughout follow up and/or continuous exposure measurements.

Power Aim 5. The sample size for this aim is based on the ability to detect a difference in the prevalence of symptoms consistent with a presumptive diagnosis of depression (PHQ-9≥10) among mothers with and without a malnourished child. Assuming 80 children develop malnutrition and 15% of mothers of non-malnourished children are identified with depression at the day 180 visit, we will have 80% power (alpha=0.05) to detect a prevalence ratio of 1.8.

14. Procedures

i. Screening and recruitment

The MAMMS study will screen mothers of infants attending 6-month and 9-month immunizations, weight visit, acute illness visits (infants aged 5 months and 14 days to 12 months and 14 days). Study staff will work closely with clinic staff at each site to determine eligibility and facilitate recruitment. Parents of eligible children will be given an overview of the study by study staff. If the mother is interested in participating, written informed consent will be obtained in a language of the mother's choosing (English, Kiswahili, Luo, Kuria).

A screening log will be maintained to capture all mother-infant pairs attending MCH clinic and will document reasons for non-inclusion. The screening log will not contain patient-identifiable information, only date, infant age, maternal literacy and access to a mobile phone will be noted. Following informed consent, a unique study number will be allocated to the mother-infant pair.

ii. Enrollment and follow up

At enrollment, all mothers will be interviewed by study staff to assess social and demographic information, medical and obstetric history, and nutritional household information. Contact information and a detailed description of the household's location will be taken to facilitate home visits and tracing of the participant for missed follow up visit. Anthropometric measurements will be obtained in duplicate using standard procedures from all children and all mothers (weight, height, and MUAC) or in triplicate if the two measures vary substantially. Maternal health status, including depressive symptoms using the PHQ-9 screening tool, the child's previous health and the family's socioeconomic status will be assessed to evaluate household vulnerability. As Migori and Homa Bay Counties are areas of high HIV prevalence and HIV-exposed infants are at increased risk of malnutrition, HIV status of all consenting mothers will be ascertained. If rapid HIV testing kits are not available for HIV testing in HIV-exposed infants, the HIV-exposed infants will be referred for HIV polymerase chain reaction (PCR) testing at the MCH department per Kenya guidelines. Newly diagnosed mothers and HIV-exposed children will be referred to Comprehensive Care Clinic (CCC) at each site for HIV care and treatment services. Following

randomization, and at the end of the enrollment visit, each mother-child dyad will receive reimbursement for transportation.

Study staff will receive training on mother-led MUAC during a Training of Trainers (TOT) supported by the developers of mother-led MUAC, the Alliance of International Medical Action (ALIMA).[43] All mother-child dyads will receive the ALIMA developed training session including videos, pictures, and practical demonstrations on how to correctly measure their child's MUAC as led by trained study staff. This training will include basic nutritional education. Following the study staff led training session, the mother will measure their child's MUAC, using an insertion MUAC tape, and the field worker will repeat the MUAC measurement (swap-validation). This swap-validation will serve as the first validation point of maternal-led MUAC assessment. If the mother fails the validation check, defined as a difference of ≥0.05 cm between the field worker and mother's MUAC measurement, then study staff will provide further instruction to the mother. Satisfactory completion of the MUAC training will be defined as three consecutive MUAC measurements <0.05 cm between the mother and the field worker, using their own child and two randomly selected children of similar age at the facility. Any mother not able to satisfactorily complete the MUAC training after receiving a second training, will be excluded from the study. The training session is anticipated to take 20-30 minutes.

iii. Randomization

After completion of enrollment procedures, including the MUAC training, each mother-child dyad will be randomized to MAMMS or SOC at 1:1 ratio (in blocks of 10) (Figure 2). Randomization allocation codes will be generated by the study biostatistician using random block sizes. Allocation codes will be placed in sequentially numbered and sealed envelopes by participant ID.

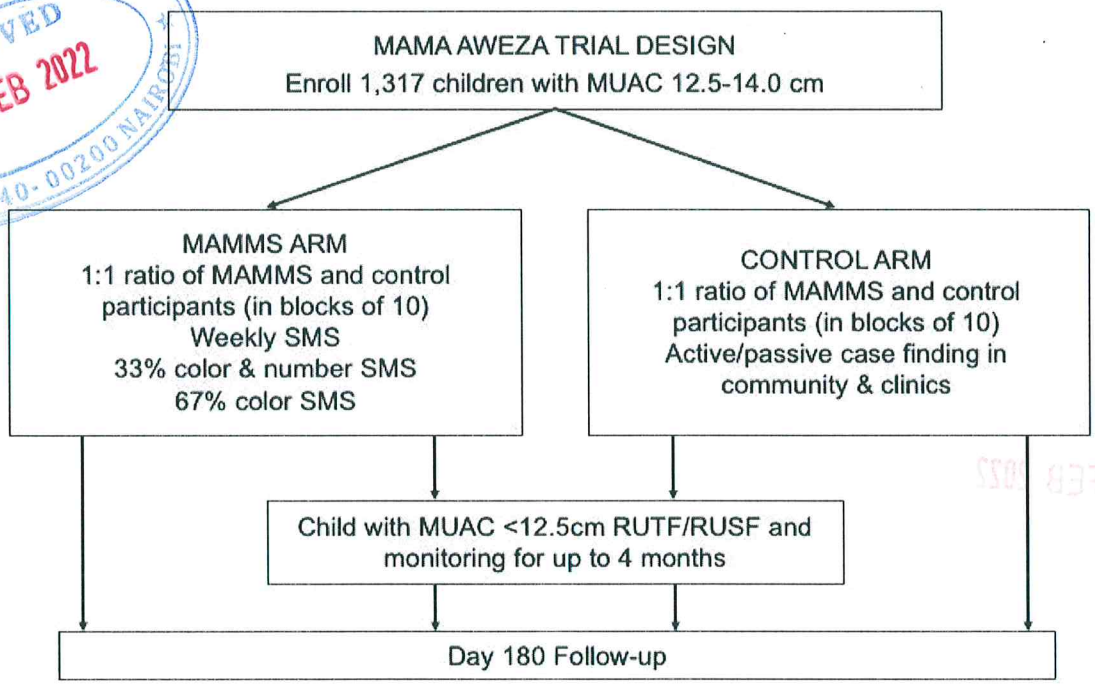


Figure 2. Randomization schema for the MAMMS trial

iv. Intervention

Once the mother has satisfactorily completed the MUAC training and undergone randomization

to the intervention arm, mothers will be provided with two insertion MUAC tapes that are UNICEF color coded and numbered to 1 mm gradations to take home with them. Mothers will be asked a series of short open-ended questions to assess their confidence in administering the MUAC and taking action upon observed measures (i.e. tool usability), their confidence that the tool can accurately assess the nutritional status of their child (i.e. perceived efficacy of the tool), and their plan for how to integrate the tool into their household routine (i.e. acceptability and perceived social acceptability of the tool). These questions will be repeated at the 180-day follow up visit to assess changes to the acceptability and feasibility of the MAMMS model associated with increased exposure and use of the MAMMS system.

v. Integration of the MAMMS platform

Development and Delivery of SMS Messages. The SMS message requesting maternal-led MUAC measurements will be designed based on findings from our preliminary SMS intervention, Mobile WACh, and our ongoing SMS intervention, Mobile Neo.[37,38,44–46] SMS messages will provide actionable reminders to measure their child's MUAC and send responses to the MUAC measurements sent by the mother. SMS messages will be translated into local dialects (Kiswahili, Luo, Kuria) and mothers will select the dialect of their choice upon randomization to the MAMMS arm.

vi. Interactive SMS Messaging

At 7 days following enrollment, mothers will receive a SMS message from the MAMMS system asking them to measure their child's MUAC and return the measurement via SMS. Mothers will receive the same SMS message asking for their child's MUAC every 7 days until the last study visit at 180 days following enrollment. Subjects are called by study staff to find out reasons that they have not sent MUAC measurements, if they are not responding. The number of calls will be

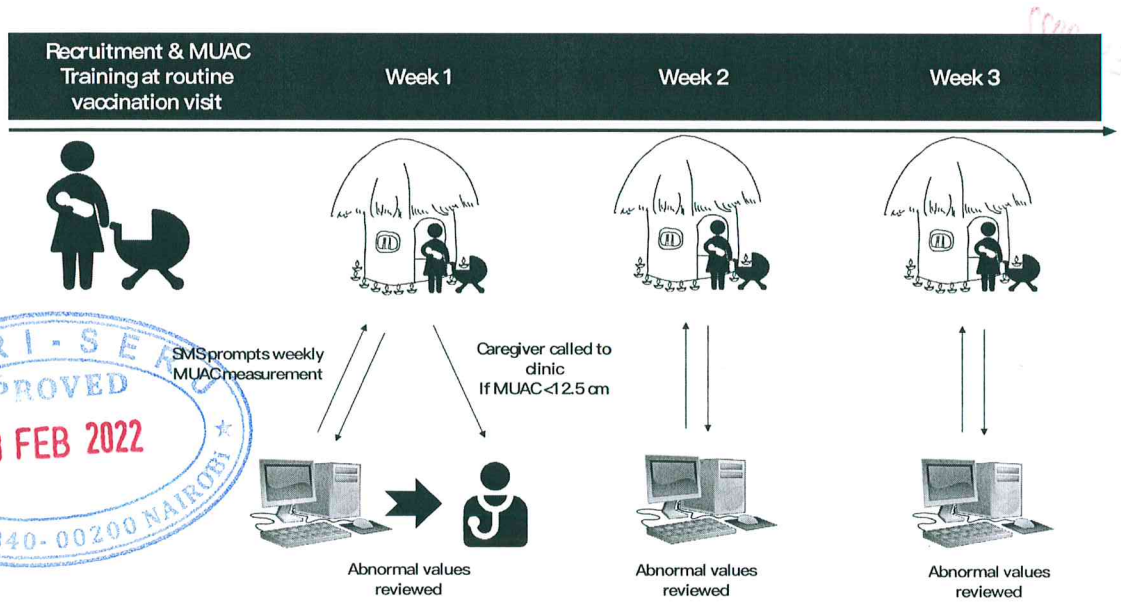


Figure 3. Outline of the MAMMS system

documented on the dashboard call log.

At the 180-day visit, mothers will complete an acceptability evaluation to help determine acceptability of mother-led MUAC and optimal timing of SMS requests for MUAC measurements. We will partner with a local premium rate service provider, Africa's Talking, to provide SMS messages (both SMS sent to the mother and SMS responses sent by the mother to the MAMMS

system) free of charge to participants. The study nurse will screen all measurements returned to the MUAC system daily (Figure 3). The MAMMS system will flag any erroneous or abnormal measurements, including MUACs diagnostic of malnutrition (<12.5 cm), or implausible values (<3 cm, >25 cm, change of >1 cm in 1 week), and the study nurse will call the mother to confirm the correct MUAC measurement. MUAC measurements within the standardized or acceptable range visit to occur in the next 1-2 days. To ensure comparability of case findings between the two arms, passive case finding will be conducted for the MAMMS arm (i.e. if a child is admitted to the paediatric ward with newly diagnosed malnutrition this will be considered as an outcome).

vii. Control (SOC) arm

Mother-child dyads randomized to the SOC arm will receive the same MUAC training and nutritional education as mothers in the MAMMS arm. To simulate the current "gold standard" community malnutrition screening program, both active and passive malnutrition identification will be conducted to identify children with the outcome (acute malnutrition defined as MUAC <12.5 cm as measured by a trained health professional). Active case identification will mirror community outreach programs in which community health workers conduct nutritional screening at various contact points including door-to-door or other central locations within the community. To accurately simulate community outreach programs, no SMS message will be sent to the mother prior to these quarterly visits.

For passive case identification, study staff will work with hospital staff at each study site to monitor hospital admissions and identify any children in the SOC arm that are admitted to the paediatric ward. In such cases, nutritional status will be ascertained at the time of hospital admission. Passive identification will be strengthened by instructing all enrolled mothers to present to the research team if they believe their child requires hospitalization, after which the study staff will escort the mother to hospital staff to ensure the child receives proper clinical attention. To capture information on admission to non-study site hospitals or receipt of malnutrition diagnosis at a different health facility, we will ask the mother whether the child was admitted to a paediatric ward or received a diagnosis of malnutrition at the day 180 follow up visit. If a hospitalization or malnutrition diagnosis occurred, a field worker will visit the appropriate clinic or hospital and ascertain a copy of the patient's notes and confirm the diagnosis of malnutrition.

viii. Post-randomization day 180 follow up visit

All mother-child dyads will return to clinic at day 180 (Figure 2). At day 180 visit, study staff will administer a standardized questionnaire to ascertain the mother's health status, including depressive symptoms using the PHQ-9, and the current condition of the child, recent malnutrition diagnosis, and other illnesses and hospitalizations. If a participant is reported to have been hospitalized or died at any time point during study follow-up period, study staff will review the participant's hospital record (if available) and complete a Serious Adverse Event (SAE) form. All hospitalized participants will be followed-up until discharge or SAE resolution. If a SAE has not resolved at the time of discharge from the hospital, the study staff will reach out to the Child's parent or caregiver to check on the physical status of the child 30 days from discharge or at day 180 study visit to closeout the SAE.

Study staff will obtain anthropometric measurements (weight, length, and MUAC) in duplicate using standard protocols from all children and mothers or in triplicate if the two measures vary substantially. Mothers in the MAMMS arm will be asked to measure their child's MUAC to serve as a comparison with day 180 MUAC measurement taken by study staff. All participants will receive a SMS reminder 3 days prior to their scheduled follow up visit. If the mother-child dyad does not return at their scheduled time, study staff will attempt to contact the mother via mobile

phone. If the mother cannot be reached, staff will trace the child to the household within 10 days of the scheduled follow up visit.

ix. MUAC validation monitoring

Following maternal report (via SMS) of acute malnutrition (MUAC <12.5 cm), study staff will contact the caregiver and request them to bring the child to the clinic for confirmation of the MUAC reading. If the caregiver is not reachable or not able to come to the clinic, we will dispatch a field worker to the home as soon as possible. During the home visit or at the study clinic, the trained field worker will measure and record the child's MUAC. The field worker MUAC validation will be used to evaluate the accuracy of the mother's report (via SMS) of her child's MUAC <12.5 cm. All children with confirmed moderate acute malnutrition (MUAC 11.0 to 12.5 cm) will be offered UNICEF adherent treatment. Should the field worker identify a child with severe acute malnutrition (MUAC <11.0 cm) or needing immediate medical attention, the child will be immediately taken to the study site for proper clinic treatment. As interim MUAC validation monitoring would not be feasible in a real-world program, comparisons between maternal and field worker MUAC measures will occur at baseline, when the mother and field worker both measure the child's MUAC, at times when the mother reports (via SMS) her child's MUAC <12.5 cm and the field worker confirms the child's MUAC, and at the day 180 visit when the mother and field worker both measure the child's MUAC.

x. Outcomes assessment

The primary outcome of this study will be time to diagnosis of acute malnutrition, defined as MUAC <12.5 cm as measured by a trained health professional. In the MAMMS intervention arm, the trained field worker will visit the house and confirm the child's MUAC when the mother has reported (via SMS) a MUAC <12.5 cm if clinic confirmation is not feasible. In the SOC arm, we will identify children with MUAC <12.5 cm during home visits or other agreed upon location conducted by the trained field worker (as part of standard active screening) or by local Migori and Homa Bay Counties' nutritionists at hospital admission or during routine active or passive screening. For the latter scenarios, we will identify malnutrition diagnoses through personal communication with the Migori and Homa Bay Counties' nutritionists and confirm the diagnosis through review of the child's medical notes during hospitalization or clinic visit. Any child identified with acute malnutrition (MUAC <12.5 cm) will be offered WHO/UNICEF adherent treatment for malnutrition (including ready to use therapeutic or supplementary food [RUTF/RUSF], deworming, screening for medical complications, and amoxicillin for children with severe acute malnutrition [SAM]). The study will collaborate with the nutritionist at each study site to organize appropriate nutritional treatment for the child. Children in both the MAMMS and SOC arm will receive the same nutritional treatment, as indicated by SAM or moderate acute malnutrition (MAM), but we hypothesis that malnourished children in the MAMMS arm will be identified earlier, require a shorter duration of therapeutic treatment and have a lower rate of treatment failure than children in the SOC arm. Study staff will follow the clinical progress of these children for four months after identification of malnutrition to ascertain treatment failure rates. If a child recovers from malnutrition and is discharged from treatment within the 180-day follow up period, they will continue with their regularly scheduled follow up visits. Maternal depression will be assessed at enrollment of their child in a CMAM treatment program and ascertained monthly during the four-month CMAM treatment regimen to see if improvements or deteriorations of the child's nutrition status are associated with changes in maternal mental health.

xi. Acceptability, feasibility, fidelity, cost and cost-effectiveness assessment

We will evaluate the acceptability, feasibility and cost of the MAMMS system using a mixed-methods assessment of mother and nutritional program worker experiences and insights. Prior to study enrolment beginning and after ethical approval, we will conduct focus group discussions with mother in vaccine clinics to allow potential future to have input into designing the platform.

The focus group discussions will also inform a short baseline questionnaire that will be administered to caregivers at enrolment. During baseline MUAC training, mothers will provide short qualitative responses to standardized open-ended questions to assess the acceptability and feasibility of the MAMMS tool. Additionally, all mothers in the MAMMS arm will be administered a survey at study completion (180 days or the time at which a child is identified as malnourished), that will use Likert scores to quantify key indicators of participant satisfaction, tool acceptability, appropriateness, and feasibility. The same short open-ended questions deployed at the MUAC training will again be asked to assess changes in acceptability and feasibility over time. Mothers enrolled in the SOC arm will also be administered a short survey at study completion to assess their satisfaction with SOC procedures, and desired level of engagement in nutritional monitoring of their children in the future. At study completion, a subset of mothers from both study arms will be selected for focus groups discussions (FGD). Focus group participants will be randomly sampled from the pool of mothers, with six mothers sampled to participate in each FGD.

Two focus groups for each of the following sets of mothers will be conducted, with eight focus groups in total (1) MAMMS participants whose child did not develop acute malnutrition, (2) MAMMS participants whose child became acutely malnourished, (3) SOC participants whose child did not develop acute malnutrition, and (4) SOC participants whose child became acutely malnourished over the duration of the study (Table 1). To complement, we will conduct in depth interviews with mothers in the MAMMS arm to assess drivers of engagement with the platform. This includes approximately 5-8 mothers who were engaged with the MAMMS platform, and approximately 5-8 mothers with low engagement. Engagement will be defined as mothers who sent SMS responses with a child's MUAC within 7 days of receiving a message. We will also conduct interviews with nutritional staff currently active in Migori and Homa Bay Counties and MAMMS staff. Individual interviews will be conducted with purposively sampled health volunteers, including up to ten community health volunteers, three nurses, three nutritionists and three nutrition program managers. The individual interviews will be used to access health worker perceptions of the MAMMS model, potential barriers to sustaining or scaling the program, and opportunities to improve the program moving forward. All FGDs and interviews will be conducted in the local language (Kiswahili, Luo, or Kuria) by a trained qualitative researcher and audio recorded for subsequent analysis. Interviews may be conducted in lieu of FGDs depending on the COVID-19 situation to respect social distancing recommendations.

Focus Group Discussions	MAMMS	SOC
Child became acutely malnutrition	2	2
Child did not develop acute malnutrition	2	2

Table 1. Subset of mothers for focus group discussions

Both financial and economic opportunity costs will be collected to determine the total incremental costs and cost per beneficiary correctly treated for MAMMS relative to standard of care. We will use a bottom-up, ingredients-based costing approach from the individual (mother and child), health system, and societal (individual and health system) perspectives. A standardized costing tool will be established and pilot tested to capture both economic and financial costs associated with each study arm, including activity-specific material and human resource costs. We will measure and present both economic and financial costs, where economic costs capture the opportunity cost of all resources used, regardless of whether these resources were donated or paid for by the project. Financial costs refer to actual monetary outlays by the project, the facility or the individual. Costs will be organized according to specific activities and inputs, as well as three primary implementation domains: 1) program administration, 2) screening of malnourished children, and 3) treatment of malnourished children. We will integrate these data with UNICEF/WHO guidelines through an ingredients-based approach to quantify the resources and unit-cost required for nutritional programs in this area. Any study measured increased coverage achieved through MAMMS, and the calculated cost-per-child treated in the intervention

arm will be combined with existing cost-effectiveness models for CMAM programs, for example the LIST model. These will also include any measure study measured improvement in treatment success after diagnosis of MAM.

Time-and-motion studies will be used in both intervention and control arms to assess the economic opportunity costs related to personnel and beneficiary time associated with each nutritional monitoring platform. During each MUAC validation visit in the MAMMS arm, study personnel will ask mothers how much time they spend measuring and sending their child's MUAC each week. The opportunity costs of nutrition staff and mothers in the SOC arm will also be assessed during time-and-motion studies to determine the amount of time that community members and health volunteers expend to deliver routine nutrition monitoring. A random sample of 10% of community visits in the SOC arm will be selected for inclusion in the time-and-motion monitoring, during which study staff will accompany the nutrition staff to monitor time and resources expended per activity. In both study arms, time-and-motion studies will be used in health facilities to assess time expenditures on caring for acutely malnourished children identified by the study. Together, these data will provide valuable information regarding the total costs of each nutrition model, accounting for the financial and economic costs that influence program sustainability.

xii. Data collection

Throughout the study, we will collect data on demographic, and maternal and infant health characteristics and outcomes on a standardised case report form (CRF) administered by trained study staff. The data will be held locally and uploaded to the secure central UW-KEMRI server in Seattle. This will be overseen by Kenya and Seattle data management team. Access to the study database will be restricted and password protected.

xiii. Provisions for data verification, and validation

The data management system, such as REDCap, will generate automated queries and data management staff will generate manual queries. All queries will be clarified by the field staff with clear documentation. The database will maintain an audit trail.

15. Limitations

This study has several limitations that may influence generalizability. While we will capture data on breastfeeding, complementary feeds, and other factors that might influence early childhood malnutrition, residual confounding may exist. The study will not cover transport costs outside of regular scheduled study follow-up visits, and as such, we may miss data on those families that do not return to the clinic outside of study follow-up visits because they cannot afford transport. However, this approach is consistent with ongoing health programs and should MAMMS found to be effective, it would not be easily scaled or sustainable if the county or national government were required to pay clinic transport. We will exclude mothers with no phone access and those who cannot read or write or have no one to help them read or write, and those who are not able to understand MUAC after training, which may exclude mothers from the poorest families with children at higher risk of malnutrition. Lastly, if the incidence of acute malnutrition is lower than anticipated, additional sites may be opened. This decision will be made under the supervision of the Data Safety and Monitoring Board (DSMB). While we anticipate high response rates, based on the >90% response observed in ongoing Mobile WACh trials, if uptake or utilization of the MAMMS platform is low, we will view this as an indication that the intervention is not viable in its current form and the DSMB will be empowered to apply all appropriate study termination rules.

A final limitation are the assumptions made in using a time-to-event analysis for Aim 1. We assume that the intervention itself will not influence the true underlying incidence of malnutrition. To avoid violating this assumption we are avoiding sending SMS messages that may reduce the

incidence of malnutrition. We will also test whether the cumulative incidence across the study arms are the same in a secondary analysis of Aim 1.

16. Data Management

i. Data Storage

Data will be entered on to de-identified paper forms which will be stored at the research site in a locked cabinet in a locked and secure study office that is accessible only by study staff. Data will be entered from the CRF to a comprehensive and secure web-based database, such as REDCap. The database will be password-protected, will not contain identifiers, and data storage and handling will follow Good Clinical Practices (GCP) at every stage. Only the investigators will have access to the data. At the end of study recruitment, when all enrolment and follow up visits are complete, study files will be securely transferred to the KEMRI-UW offices at KEMRI Headquarters off Mbagathi Road in Nairobi. In Nairobi, the files will be stored in locked cabinets in a locked and secure KEMRI-UW office for three years after the data has been cleaned and the primary manuscript published. Thereafter the physical files will be destroyed.

A participant identifier link log will be kept at the site in a locked cabinet in the study office and will be the only link between patient identification numbers and identifiable data. All study staff are trained in data protection and privacy and are required to have certified CITI training in human subjects' research.

ii. Data Management

The data staff at the UW-KEMRI study site office(s) will be responsible for receiving, entering, and cleaning data in the study database and responding to data queries. The data management teams in the UW-KEMRI offices in Migori, Homa Bay, Nairobi, and Seattle will undertake checks, querying, analysing and storing all data that accrues from the study. The University of Washington will serve as the custodian of the database. The data will be available to the KEMRI PI and all co-investigators involved in the study. Requests to access the data from other investigators will be reviewed by the UW and KEMRI PIs as well as the MAMMS co-investigators.

iii. Analysis

The primary outcome of this study will be time to diagnosis of acute malnutrition defined as MUAC <12.5 cm as measured by a trained health professional. Only the first detection of acute malnutrition will be included in the primary analysis, i.e. no repeated outcomes. Any child first identified with acute malnutrition by the trained field worker at the day 180 study termination visit (MAMMS or SOC arm) will be considered missed diagnoses and not counted in the primary outcome. Any children identified with acute malnutrition as measured by trained field worker will receive treatment for acute malnutrition and be enrolled in the treatment phase of the study. Secondary outcomes will include the proportion of children who recover from acute malnutrition following diagnosis and treatment and all-cause mortality and all-cause re-hospitalization between study arms. Within the MAMMS intervention arm, we will also evaluate the sensitivity and specificity of maternal MUAC measurements, and the acceptability, feasibility and cost per-child-treated. We will evaluate prevalence of depression among mothers of children with malnutrition, we will evaluate prevalence of depressive symptoms at enrollment of their child in a CMAM treatment program and monthly during the child's four-month treatment regimen to understand the relationship between maternal depression and the child's nutritional recovery.

115 children were administratively censored due to COVID-19. These children have complete baseline data and some incomplete follow-up information. In keeping with the original consent, we will use this data in future analyses, where the COVID-19 disruptions that affected these children do not bias the study.

Aim 1: Determine if MAMMS leads to earlier identification and recovery from acute malnutrition (MUAC <12.5cm). Primary analyses will be intent-to-treat (ITT) based on randomization allocation to MAMMS or SOC arms. All statistical analyses will be performed using Stata and R statistical packages. To ensure randomization was successfully balanced between arms, baseline characteristics will be compared using a Chi-square test for dichotomous variables and Mann Whitney U test for continuous variables. Reasons for exclusion from the trial, including the inability to provide a mobile phone number and those that could not read or write and did not have someone to help them read or write, will be detailed in the CONSORT flow diagram. While we anticipate successful randomization to result in no important baseline differences between arms, should we identify any chance imbalance in baseline characteristics, we will evaluate these variables as potential confounders in a sub-analysis secondary to the ITT analysis. To determine whether the MAMMS arm can identify acute malnutrition earlier than the SOC arm, we will use Cox proportional hazard regression models to conduct a time-to-event analysis, with acute malnutrition (defined as MUAC <12.5 cm) being the event. Kaplan-Meier plots will be used to graphically depict the survival probability against time. In addition, we will compare the proportion of children with malnutrition (defined by MUAC, weight-for-length Z-score [WLZ] and nutritional oedema) that were not on treatment between study arms (i.e. screening coverage). Secondary analysis will compare time to recovery from acute malnutrition by randomization arms as follows: time zero (T0) will be set as the date of study staff confirmed diagnosis of acute malnutrition and recovery (event) will be defined as WLZ >-2 and/or MUAC ≥12.5cm for two consecutive measurements two weeks apart, as per Kenyan guidelines.[47] To evaluate the association of literacy and mobile phone ownership with study outcomes, we will stratify results by caregiver literacy (literacy level assessed in the consent process) and mobile phone ownership (owned by caregiver, family member, friend or other). Recovery rates will be compared between arms using Cox proportional hazard models in an ITT analysis. We will also compute the incidence of all-cause mortality and all-cause re-hospitalization between study arms, although we anticipate that these events will be rare.

Aim 2: Demonstrate the accuracy of maternal administered MUAC assessments compared to trained community health worker, and the ability of repeated maternal administered MUAC measurements to monitor early childhood growth. To determine the accuracy of maternal MUAC measures to field worker measures taken on the same child, we will calculate the Pearson's correlation coefficient and compare the mean difference in maternal and field worker MUAC measures at enrollment and the day 180 study termination visit. We will also calculate the average bias, sensitivity and specificity of maternal and field worker MUAC measures at enrollment (following MUAC training), at times when the mother reports (via SMS) her child's MUAC <12.5 cm and the field worker confirms the child's MUAC, and maternal and field worker MUAC measures taken at the final day 180 visit. In secondary analyses, we will use generalized linear mixed effects models to determine whether the quality (measured as the correlation between maternal and field worker MUAC measures) of maternal measurement decreases over time, with time included as the time from enrollment and day 180 visit and times when the mother SMS reports MUAC <12.5 cm and the field worker confirms maternal MUAC, if applicable. In exploratory analyses, we will generate a phenotypic profile of children at high-risk of malnutrition using repeat MUAC measures from children in the MAMMS arm. We will first generate longitudinal MUAC trajectories using weekly data collected from enrollment to either day 180 or development of acute malnutrition and then apply supervised computer-learning to plot MUAC trajectories predictive of acute malnutrition.

The computer learning models will be based on incremental decreases in MUAC using data from repeat MUAC measures, the time-period over which MUAC declines, and any additional information that modifies the relationship between MUAC trajectory and development of acute malnutrition (e.g. feeding status, HIV exposure, age). As seasons are an important determinant of malnutrition, we will code each month into a priori wet and dry seasons, based on rain patterns during the study period, and include these seasons in the model building process, testing for association and interactions between seasons and MUAC trajectories. During exploratory analysis using computer learning models, missing MUAC measures will be imputed from available data.

Aim 3: Evaluate the acceptability, feasibility, fidelity and cost per-child-treated of MAMMS relative to standard-of-care nutrition programs. Acceptability, feasibility & fidelity: In this study, the term "fidelity" reflects consistent and per protocol delivery of essential components of the intervention and their associated process outcomes. It is important to track intervention fidelity to ensure that the intervention is scalable in the Kenyan setting and feasible to replicate across other geographic settings. Additionally, fidelity assessments provide an indication of the strength of the association between the intervention and targeted outcomes. In this study, intervention fidelity is defined according to three categories (1) treatment delivery, (2) treatment receipt, and (3) technology acceptance.[48] Fidelity to treatment delivery will be measured as the proportion of messages that are successfully delivered to a participant's mobile phone (based on automated tracking) and the proportion that are opened. Fidelity to treatment receipt will be measured as the proportion of delivered messages that are responded to as well as average monthly changes in responsiveness over time (i.e. attenuation). Fidelity to technology acceptance will be measured as the proportion of caregivers who come to health facilities when messaged to do so as well as the proportion of mothers who report a continued interest in participating in the MAMMS intervention during end-line acceptability assessments. All measures of fidelity will be stratified by mobile phone ownership and maternal literacy (Aim 1).

At day 180 visit, mothers in both arms will be asked to complete a survey to assess the acceptability and feasibility of MAMMS. Results will be described using standard descriptive statistics. Thematic coding of key themes will be used to analyse open ended questions that are asked at enrollment and day 180 in the both arms. The frequency of key themes will be quantified. Survey and thematic findings will be used to inform standardized question guides for FGDs and individual interviews conducted at day 180. Audio transcripts from FGDs and interviews will be transcribed verbatim in the local language and translated into English. Random quality assurance spot checks will be conducted on all transcripts and translations. A mix of in vivo open coding and thematic coding from a start list will be used to identify key themes in the qualitative data. Coding will take place using an internationally accepted qualitative data analysis program, such as Atlas TI or NVivo10 software by two independent coders.

Incremental Total cost and cost-per-child: Economic and financial costs will be reported as the incremental total costs and the unit cost per case identified and the incremental unit cost per treatment delivered over the duration of the study and presented separately for each randomization arm. We will also look at cost profiles that highlight the major components of increased incremental costs of introducing MAMMS into existing nutrition services.

We will then develop cost-effectiveness models to project the cost and health outcomes of the program over a 5-year period and estimate the incremental cost-effectiveness of the MAMMS program relative to the standard of care in terms of childhood deaths, hospitalizations, and disability-adjusted life years (DALYs) averted. Two cost-effectiveness will be built, the first will assume that MAMMS increases screening coverage to the extent measure in the study (under aim 1) but does not affect the outcome of treatment (i.e. death,

re-hospitalization or treatment failure) after identification of MAM. The second model include any observe effect MAMMS has on treatment success, as measured under hypothesis 1.2. The cost of adverse outcomes, such as hospitalization and death, will be drawn from our ongoing research in this region including the Childhood Acute Illness & Nutrition Network and the Toto Bora Clinical Trial in Western Kenya.[49,50] Cost-effectiveness is defined as the net costs (intervention costs minus treatment costs averted) over the net benefits of using MAAMS compared to the SOC. Costs will be discounted at 3% per year and sources of uncertainty will be explored in univariate and probabilistic sensitivity analyses. Sensitivity analyses will also be conducted to identify potential opportunities to maximize the cost-effectiveness of the MAMMS program in future program iterations.

Aim 4: Determine the relationship between maternal sociodemographic and health characteristics and childhood acute malnutrition. Univariate and multivariate cox-proportional hazard models will be built using data from the SOC arm of the study. Exposures of interest will include maternal factors (e.g. health, mental health, socioeconomic standing), household factors (e.g. economic status, water and sanitation), and child health (e.g. birth history, known chronic conditions) at baseline. The outcome of interest will be nutritional status, defined as developing moderate acute malnutrition or change in MUAC. We do not expect to observe substantial mortality in this study, however if deaths or other competing risks such as hospitalization are observed, the association with these risks and exposures of interest will be explored and accounted for in the analysis.

Aim 5: Determine the prevalence of maternal depressive symptoms at enrolment of their child in a CMAM treatment program and the association between maternal depression and attendance at routine CMAM visits and child outcomes. Among mothers of children identified with malnutrition, prevalence of mild and moderate/severe depression will be calculated at enrolment of their child in CMAM treatment program and monthly during the four-month treatment regimen. Mild depression will be defined as PHQ-9 score of ≥5 and moderate/severe depression will be defined as a score of ≥10. Prevalence of depressive symptoms during the treatment period will be compared to the mothers PHQ-9 score at enrolment in the study using linear mixed effect models. Generalized estimating equations clustered by subject will assess the association between PHQ-9 scores and the mother's ability to retain nutrition education and attend CMAM visits through pre- and post-nutrition education knowledge assessments, clinic attendance records, and child's nutrition status measured by MUAC. Adjusted models may include potential confounders related to: child (age, sex, malnutrition severity, medical complications, HIV status), caregiver (age, sex, MUAC/BMI, illness, HIV status, marital status), socioeconomic (food security, asset index, improved sanitation and water source), and site.

17. Intellectual Property

Any intellectual property rights that arise from the work will be safeguarded according to current KEMRI guidelines and the Industrial Property Act of 2001, sections 32, 58 and 80. The scientific and intellectual contributions of all persons involved in the research will be appropriately acknowledged in all publications and presentations arising from the work.

18. Time Frame/Duration of the Project

	Yr 1			Yr 2			Yr 3					
Protocol & questionnaire design, ethic approval	◆	◆										
MAMMS platform software development	◆	◆										
Staff hiring and training		◆										
Recruitment, enrolment			◆	◆	◆	◆	◆					

Follow-up			◆	◆	◆	◆	◆	◆	◆			
Treatment of malnutrition			◆	◆	◆	◆	◆	◆	◆	◆		
Interim analysis							◆					
Data cleaning				◆	◆	◆	◆	◆	◆	◆	◆	◆
Manuscript development and submission										◆	◆	◆

The study will begin as soon as scientific and ethical approvals are granted, and we anticipate this study will take 4 years to complete. We have begun to develop clinical protocols and data collection tools, and will finalize these documents and apply for and obtain ethical approvals during the first 6 months of the award. Adaptation of the MAMMS platform will occur during the first 6 months of Year 1. We will also begin sensitization at the clinic sites to ensure the community is aware of the purpose of the project. Field site preparation, including hiring and training of site staff, will be complete by the end of Year 1. We will enroll participants and complete follow-up visits within a 24-month period in Years 2 and 3. Data cleaning will be ongoing and data analysis and manuscript development will continue for an additional 24 months.

19. Ethical Considerations

This protocol will be subject to ethical approval from SERU, KEMRI, Nairobi; and the IRB at the University of Washington, Seattle, USA.

a) Human Subjects

First do no harm; the study will maintain ethical standard through internal and external training, monitoring and standardisation of procedures.

i. Risks and Adequacy of Protection Against Risks

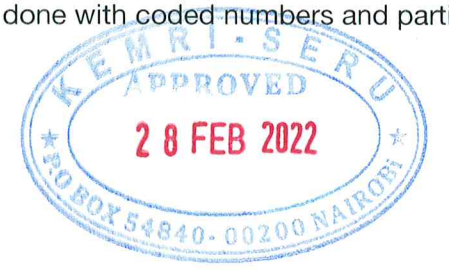
There will be minimal risk to subjects. Potential disclosure of confidential information relating to maternal and child health and HIV status, but all necessary steps will be taken to ensure data remains secure and confidential. All personnel involved in the study will be trained in research participant confidentiality and data security and GCP will be followed at all stages of data handling. Potential disadvantages for participants also include the time taken to attend 180 day follow up and answer questions. Mothers may become nervous about measuring their child's MUAC, but training in MUAC measurement will be implemented to help avoid this problem. Mothers will receive reimbursement for their time and travel expenses at enrollment and day 180 follow up visit. We anticipate there will be no incidence of explicit or implicit harm to participants.

ii. Benefits to the Participants and Community as a whole

Mothers will benefit from a short counselling session about child nutrition and learning how to use MUAC tapes. Children who are diagnosed with acute malnutrition will receive standard treatment per Kenya guidelines. All children will receive a free child health check at day 180 follow up visit. The communities in this study have a high prevalence of undernutrition. Findings from the MAMMS trial are expected to lead to improvements in the diagnosis and management of childhood malnutrition which would directly benefit the communities involved in this study and generate findings relevant to improving the early identification of malnutrition among children in resource-limited settings.

iii. Confidentiality

Every effort will be taken to maintain participant confidentiality through dedicated implementation of GCP principles. All CRFs will be kept in a locked filing cabinet at the study site, which is accessed only by the investigators and the study staff. All computer entry and networking programs will be done with coded numbers and participant's initials only. Only the



investigators will have access to these records. Only de-identified data will be shared with the funder or other investigators, as specified under the section on data sharing.

iv. Community Engagement Strategy

We will engage hospital administration at each of the MCH clinics from which mother-infant pairs are recruited. Through hospital management, we will introduce the study to the Matron In-Charge and other health volunteers in the MCH clinic. Community sensitization will be undertaken through establishment of a Community Advisory Board (CAB) designed to help disseminate information about the study. Members of the CAB will represent the villages in Migori and Homa Bay Counties, and the CAB will meet every 6 months. Following each CAB meeting, the CAB members disseminate study information to the local communities.

Community sensitization will initially be undertaken through the existing KEMRI/UW CABs in Migori and Homa Bay Counties. Members of these CABs represent 75% of the villages in Migori and Homa Bay Counties. The CAB members will meet initially at the introduction of the new (MAMMS) study for the members to familiarize themselves with the study, and thereafter, every 6 months. Following each CAB meeting, the CAB members will be facilitated to disseminate study information to the local community.

Stakeholder information giving

The key stakeholders in this study are the hospitals hosting the study, the community engaged in the research, the Ministry of Health, the investigators and the funders. Written and oral information regarding the study's purpose and processes will be given to each of these parties. The Migori and Homa Bay communities will be informed of the study by members of the CAB, as described in the community engagement strategy. The site PIs and the scientific leads will meet local hospital and Ministry of Health officials to inform them of the study prior to the beginning of the study. The funders will be engaged through regular progress reports given by the scientific leads.

v. Individual informed consent process

The study will be carried out in conformity to the ICH-GCP principles for informed consent. These principles will be stated and explained clearly in informed consent SOPs. This will be the basis for training staff involved in obtaining informed consent. The mother will receive an explanation of the study by a member of the study team in private and in an appropriate language (Kiswahili, Luo, Kuria, English) during enrollment. Mothers will be given a chance to ask questions before written permission to be included in the study is sought. Mothers who are unable to write will be asked to provide a witnessed thumbprint in the presence of an impartial third party. Informed consent will be required from health workers participating in individual interviews. Consent will be obtained in a private location in each participating health facility. Consent will only be obtained when the potential participant understands their duties as a participant and all of their questions and concerns have been addressed by study staff, and they provide written consent to take part.

vi. Training/support for those involved in community engagement and administering consent.

On-site training in community engagement and consent will be given to all study staff prior to enrollment beginning. All persons administering consent will have research ethics and GCP training.

vii. Feedback of information

Results of the study will be fed back to the study communities through each research institution's community representatives, public meetings, hospital and counties involved and

the follow up clinics in each site. Results will be shared through presentation at local and international scientific meetings.

b) Animal Subjects
Not applicable

20. Expected Application of the Results

MAMMS is an innovative, low-cost and low-risk intervention with the potential to dramatically increase the number of children identified and treated for malnutrition and, in turn, substantially reduce malnutrition associated deaths. These results will inform a step-wedge cluster randomized trial of regional (western Kenya) MAMMS implementation to test the feasibility of scaling up the MAMMS program. We hope to achieve widespread MAMMS implementation within 6 years of this protocol being completed.

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22. Budget

Below are estimated costs of conducting the study. The cost in Kenyan shillings (KSH) is based on an exchange rate of 100 KSH = 1 USD.

Budget	Total (USD)	Total (KSH)
Personnel:		
Coordinator	36,317	3,631,700
Fieldworker	10,530	1,053,000
Fieldworker	10,530	1,053,000
Fieldworker	10,530	1,053,000
Fieldworker	10,530	1,053,000
Fieldworker	10,530	1,053,000
Supplies	26,985	2,698,500
Equipment	0	0
Travel	15,600	1,560,000
Community Mobilization	420	42,000
Participant Costs	12,600	1,260,000
Staff Training	3,250	325,000
Translations	250	25,000
Dissemination Meetings	150	15,000
Administrative overhead	11,858	1,185,800

23. Justification for the Budget

Personnel:

TBN, Study Clinician Coordinator, will liaise directly with field workers, investigators, and clinic administration to ensure staff and study procedures are in place and being followed. S/he will be involved in data collection including recruitment, screening, consenting, enrollment, data entry and follow up of participants. S/he will devote 70% effort for 12 months in Year 1, 100% effort in Year 2, and 25% effort in Year 3.

TBN, Field worker (5), will be involved in participant recruitment, screening, data entry, and follow up. Field workers will each devote 50% effort for 12 months in Year 1, 100% effort in Year 2, and 25% effort in Year 3.

Field costs, training and participant reimbursement:

The cost of travel for field workers to participants in the community will vary between sites, depending on distance from the hospital, and logistics of transport. Similarly, participant reimbursement will depend on distance and cost of attending hospital.

24. Investigator Roles and Responsibilities

	Study Design	Training	Site evaluations	Liaise with Ministry of Health	Information & Consent	Supervision of data collection	Data management	Statistical analyses	Data interpretation	Report writing
Dr. Christine McGrath	X	X	X	X		X		X	X	X
Dr. Kirk Tickell	X	X	X	X		X		X	X	X
Dr. Jennifer Unger	X	X					X	X	X	X
Dr. Benson Singa	X	X		X		X			X	X
Dr. Arianna Rubin-Means			X						X	X
Dr. Barbra Richardson	X							X	X	X
Dr. Joyce Akuka		X	X	X						X

25. Appendices

Appendix A: Ethics certificate of each investigator
Appendix B: CVs of non-KEMRI investigators
Appendix C: CRF
Appendix D: Consent form
Appendix E: ALIMA training materials
Appendix F: Focus Group Discussion and In-Depth Interview tools

Appendix A: Ethics Certificate of Each Investigator

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