Clinical Study Protocol

Effectiveness of an integrated programme to reduce maternal and child malnutrition in Kenya

Study Identifier: GW_1AF_KenEff

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ABSTRACT

Background: In Kenya, 26% of children under-five years of age are malnourished, and 26% of pre-school children, 26% of women of reproductive age and 42% of pregnant women are anaemic, respectively. Agriculture is the main source of income and food for the majority of rural families in Sub-Saharan Africa including Kenya. Agricultural programmes have led to increased yield and household income but had limited success in improving nutritional status.

Objectives: To assess the impact on growth and micronutrient status of an integrated programme by introducing nutrition-specific (e.g. micronutrient supplements) and nutrition-sensitive (improved water, sanitation and hygiene, e.g. chlorine, soap) components to an existing agricultural programme.

Methods: The impact of the integrated programme will be assessed in two cluster-randomized intervention studies comparing one group receiving the integrated intervention to another group receiving the agricultural intervention alone (control arm):

Study 1: cluster-randomized, parallel-group, prospective, follow-up effectiveness study in pregnant women and their offspring

Study 2: cluster-randomized, parallel-group, prospective, follow-up effectiveness study in children 6-59 months old

Study duration: The fieldwork of study 1 will take place over approximately 2.5 years (April 2018-December 2020), while the duration for study 2 will be approximately 2 years (February to 2018-March 2020).

Budget: The budget for conducting the two studies is $ 2,055,458.

ABBREVIATIONS

1AF	One Acre Fund
AE	Adverse Event
AGP	Alpha 1- acid glycoprotein
AMREF	African Medical & Research Foundation
BMI	Body mass index
CHV	Community Health Volunteer
CIFF	Children´s Investment Fund Foundation
CRP	C-reactive protein
ESRC	Ethics & Scientific Review Committee
FANTA	Food and Nutrition Technical Assistance
FAO	Food and Agriculture Organization
GA	Gestational age
HAZ	Height for age z- score
Hb	Haemoglobin
HC	Head circumference
IYCF	Infant and Young Child Feeding
KAP	Knowledge, attitude and practices
KEK	Kantonale Ethikkommission (Cantonal Ethics Committee)
LAZ	Length for age z-score
LNS	Lipid-based Nutrient Supplement
MNP	Micronutrient Powder
MUAC	Mid-upper arm circumference
ORS	Oral rehydration solution
PI	Principal Investigator
RAE	Retinol activity equivalent
RBP	Retinol binding protein
RDA	Recommended daily allowance
SAE	Serious adverse event
SDG	Sustainable development goal
SF	Serum ferritin
SOP	Standard Operating Procedure
TfR	Transferrin Receptor
UNICEF	United Nations Children's Fund
WASH	Water, Sanitation and Hygiene
WFP	World Food Programme
WHO	World Health Organization
WHZ	Weight for height z-score

1. BACKGROUND

Malnutrition, and particularly malnutrition in children under 5 years of age, remains a public health problem in many areas of the world [1]. A diet low in diversity and micronutrient density is one contributing factor while a second factor is poor water, sanitation and hygiene (WASH) practices often leading to diseases such as persistent diarrhoea and resulting in morbidity and mortality in children under 5 years of age. According to the WHO World Health Statistics 2017 that are monitoring health in order to reach the Sustainable Development Goals (SDGs) [2] including data from between 2006 and 2015, the global under 5 mortality rate per 1000 live birth is 42.5 and is clearly highest in the African Region with 81.3 while in Kenya it is lower than the African average with 49.4. The picture is similar for maternal mortality with 216 per 100,000 live births globally but with the highest in the African region with 542 and 510 in Kenya.

The statistics also look at several WASH indicators. The mortality rate attributed to exposure to unsafe WASH services per 100,000 populations is clearly highest in the African region with a burden of 43.1, while the global burden is at 12.4, and with Kenya slightly below the African burden with 32.5. In line with this, two additional WASH indicators demonstrate the poor status in the African region. The use of improved drinking water source is lowest in the African region with 68%, while globally 91% use an improved source and in all the other WHO regions it is over 90%. Kenya is slightly below the African average with 63% using an improved drinking water source. Looking at sanitation the use of improved sanitation is lowest in the African region with only 32% and is similar at the Kenyan level with 30% while globally 68% use improved sanitation. The most recent Kenya Demographic and Health Survey in 2014 estimates that only about a third of households in Kenya have washing places at their homes [3]. Also, nationally, three out of four households share toilets with other households or have unimproved toilets (open defecation, open latrines, etc.). Malnutrition is specifically covered in SDG Target 2.2 (By end 2030, end all forms of malnutrition, including achieving, by 2025, the internationally agreed targets on stunting and wasting in children under 5 years of age, and address the nutritional needs of adolescent girls, pregnant and lactating women and older persons). The WHO statistics indicate a worldwide problem with 22.9% of children under 5 years of age stunted and 7.7% wasted. While the Africa Region (33.5% and 7.4%)) together with the South-East-Asia Region (33.8% and 15.3)) have the highest stunting and wasting prevalence, respectively, the prevalence in Kenya is below the Africa average with 26.0% stunted and only 4% wasted.

Anaemia, resulting from an inadequate intake of iron and/or low iron bioavailability from the diet as well as from other causes like diseases such as malaria and other micronutrient deficiencies, has been shown to be of public health significance worldwide, particularly in preschool children and women of reproductive age. The Global Burden of Disease study in 2015 estimated that anaemia was the impairment that affected the greatest number of people in 2015 with 2.36 billion individuals affected [4]. Looking at years lost due to disabilities worldwide, iron deficiency anaemia ranks fourth. The 2013 Global Burden of Disease study estimates that 27% of the world's population was anaemic with low-income countries accounting for more than 89% of the burden [5]. Iron deficiency is estimated to be the dominant cause of anaemia worldwide with > 60%. The Kenya National Micronutrient Survey of 2011 [6] and the most recent Demographic and Health Survey in 2014 [3] show that 26% of pre-school children, 26% of women of reproductive age and 42% of pregnant women were anaemic. The prevalence of iron deficiency in children was 21.8% (serum ferritin <12µg/L after being adjusted for inflammation), and that of iron deficiency anaemia was 13.3%. In non-pregnant women of reproductive age, 21.3% were iron deficient (serum ferritin <15µg/L after inflammation adjustment) and 14.0% suffered from iron deficiency anaemia. These values were higher in pregnant women with 36.1% and 26.0%, respectively. The prevalence of vitamin A deficiency based on retinol-binding protein was highest in pre-school age children with 9.2%.
Anaemia can result in several health consequences, starting in very early live such as impaired development of the brain in the foetus and early infancy, impaired immune system and increased infant mortality as well as reduced physical capacity and work performance in adults [7]. Anaemia is in general much more amenable to prevention and treatment than many other conditions such as diabetes or cardiovascular disease but supplementation strategies have failed in many countries. Using a integrated approach delivering micronutrients to pregnant women and young children through a platform that already exists together with other interventions such as WASH that contribute to the prevention of childhood malnutrition might be a promising way forward.

The present project will use the One Acre Fund (1AF) agriculture platform to add nutrition-specific and nutrition-sensitive interventions to the agricultural intervention already in place in western Kenya.

Agriculture is the main source of income, food and nutrients for the majority of rural families in Sub-Saharan Africa including Kenya. Most rural families in Sub-Saharan Africa are smallholder farmers, and rely on agricultural produce for income and direct consumption. Despite the fact that these households are food producers, research has shown that rural farming households are typically net food consumers and are more vulnerable to malnutrition [8]. Decades of investments in the agriculture sector have focused on improving yields and income but have notably failed to improve the nutrition status of farming families and their children [9]. Since 2006, 1AF has been providing a bundle of services and agricultural inputs to smallholder farmers using a model where farmers take loans to pay for inputs and services received. The core service bundle includes environmentally appropriate seed and fertilizer, physical delivery of inputs, training, and small loans. 1AF currently reaches 445,000 farming households in Kenya, Burundi, Rwanda, Tanzania, Malawi, and Uganda. Kenya was 1AF's first country of operation and their activities will soon cover all of Western and Nyanza Provinces, which are the primary food-producing regions and hold one third of Kenya's population. The most recent 1AF report impressively shows the increasing number of farm families served, the Dollar gain in farmer impact and the close to 100% farmer repayment rate of credits for seeds and fertilizers [10].

In partnership with the Children's Investment Fund Foundation (CIFF), 1AF aims to introduce nutrition-sensitive and nutrition-specific components into the services offered to smallholder farmer households. The nutrition-specific interventions consist of providing lipid-based nutrient supplements (LNS) to pregnant women up to 6 months after delivery and LNS to their offspring from 6-24 months of age in one study and providing MNPs (Micronutrient Powders) to children 6-59 months of age in a second study. These nutritional supplements are recommended by WHO in areas where micronutrient deficiencies and malnutrition are prevalent [11,12]. In order to increase protein consumption, raw eggs (to be used for cooking) will be provided to pregnant women and up to 6 months post partum and to their offspring from 6-24 months of age in study 1 and chicken birds to households in study 2. Study 2 households will also be provided with seeds for red onion and indigenous greens. Further, children older than 6 months will be provided with oral rehydration salts (ORS) and zinc supplements as recommended by WHO and UNICEF for the treatment of acute diarrhoea [13]. As a nutrition-sensitive intervention, pregnant women will receive albendazole as preventive anthelminthic treatment after the first trimester as recommended by WHO in endemic areas [7,14]. Lastly, some WASH related interventions will also be provided, such as training sessions, soap for hand washing and chlorine for drinking water treatment.

To test the incorporation of nutrition services in 1AF's agricultural programme, pilot projects in western Kenya will be conducted between 2017 and 2020. These interventions are relevant to western Kenya where anaemia, micronutrient deficiencies, and under-nutrition are public health concerns [3,15]. The dietary diversity, food frequency and subsequently, a minimum acceptably dietary quality for young children are lower in the Western Province than for the national average. Further, the number of households with washing places is lower and diarrhoea prevalence is slightly higher compared to the national average [3].

In order to monitor and evaluate 1AF's programmes, two studies were designed to be conducted in the Western Province of Kenya and are presented here as study 1 and study 2:

- **Study 1:** a cluster-randomized, parallel-group, prospective, follow-up effectiveness study that will span over the "1,000 days window", the period from conception until the child's second birthday
- **Study 2:** a cluster-randomized, parallel-group, prospective, follow-up effectiveness study in children 6-35 months of age at recruitment that spans over 2 years

In both studies, clusters will be randomly assigned to either have the regular 1AF agricultural intervention package (already in place in all clusters participating in the study and therefore called control) or the integrated intervention package that on top of the agricultural package consists of nutrition-specific (such as providing additional micronutrients) and nutrition-sensitive (such as providing soap for hand washing) interventions. The impact on malnutrition and programmatic 'success' will be evaluated.

While in both studies the primary purpose is to longitudinally compare the changes of biological indicators such as growth and anaemia between the intervention and control group, the programmatic aspects such as adherence to and coverage of the intervention package and possible links to changes in dietary patterns and ultimately linear growth will also be evaluated.

2. PROBLEM STATEMENT

Agriculture is the main source of income, food and nutrients for the majority of rural families in Sub-Saharan Africa including Kenya. Most rural families in Sub-Saharan Africa are smallholder farmers, and rely on agricultural produce for income and direct consumption. Despite the fact that these households are food producers, research has shown that rural farming households are typically net food consumers and are more vulnerable to malnutrition [8]. Decades of investments in the agriculture sector have focused on improving yields and income but have notably failed to improve the nutrition status of farming families and their children [9].

Young children < 5 years of age and pregnant women are the most vulnerable groups when it comes to malnutrition as both population groups have an additional need for macro- as well as micronutrients to ensure proper development and growth of the child or foetus, respectively [16,17]. Single nutrition-based, health-based or agriculture-based strategies have so far not resulted in reducing malnutrition and micronutrient deficiencies significantly. In the present project, we will use an integrated approach combining agriculture with nutrition-specific and nutrition-sensitive interventions and compare it to an agriculture intervention alone. Most of the planned interventions are targeted to the pregnant women and/or children < 5 years of age directly while some interventions are targeted to the household (e.g. soap for hand washing).

The project will be conducted in the Western Province of Kenya, which is, together with the Nyanza Province, the primary food-producing region and they together hold one third of Kenya's population. The planned interventions are relevant to western Kenya where anaemia, micronutrient deficiencies, and under-nutrition are public health concerns [3,15]. If the integrated approach proves to be efficient in reducing malnutrition and micronutrient deficiencies in young children in a farming population, it could be replicated in the other regions of Kenya or countries where 1AF is active with their agricultural programme (Burundi, Rwanda, Tanzania, Malawi and Uganda). Further, the programme could potentially be expanded to other subsistence farming areas in Africa and on other continents with similar climatic conditions. By reducing malnutrition, young children will be less susceptible to infectious diseases and therefore develop better both, physically but also mentally, as they will miss fewer classes at school. By reducing micronutrient deficiencies and anaemia, children will be more active and perform better at school, which will result in an adult population with a higher level of education and likely a higher level of work productivity as practices learned during the training sessions in the intervention on safe WASH and nutrition might be integrated into daily live into adulthood.

3. REVIEW OF LITERATURE

Several agricultural programmes have tried to decrease the prevalence of undernourishment (inability to acquire enough food to meet dietary energy requirements) in the past decades. Such programmes are likely to have contributed to the reduction in undernutrition from 18.6 to 10.8% worldwide and the reduction from 27.6 to 19.8 in Africa between 1990 and 2016 [14]. The recent data indicate that Kenya has the fourth highest number of undernourished people in Africa. However, decreasing the prevalence of undernourishment doesn't necessarily mean an improvement in the malnutrition situation. Numerous studies have been undertaken to document knowledge of the effects of agricultural development projects on human nutrition. A recent publication taking into account 9 reviews published between 2001 and 2012 comes to the conclusion that evidence of agricultural interventions for impacts on nutrition is weak and mixed at best [18]. Although there is clear evidence that investment in agricultural technologies has, on average, improved yields, increased caloric consumption, and/or increased incomes, there is still confusion about the mechanisms through which agriculture can enhance nutritional status. It might be that agriculture alone is not sufficient as the topic of malnutrition is too complex and involves many other areas such as the consumption of a nutritionally diverse diet and adequate WASH practices and health care systems that are accessible and affordable for all.

Many studies have looked into the effect of nutrition-specific interventions such as providing multiple micronutrients to vulnerable population groups. Such nutritional supplements are recommended by WHO in areas where micronutrient deficiencies and malnutrition are prevalent [11,12]. Two recent trials conducted in Ghana and Malawi have demonstrated the positive effect of LNS given during

pregnancy resulting in increased weight, length and head circumference at birth as compared to women receiving iron and folic acid supplements [19,20]. One study, conducted in Bangladesh, has demonstrated the positive effect of LNS provided during pregnancy and infancy on child linear growth and head circumference [21]. There is clear evidence on the efficacy and effectiveness of the use of MNPs with respect to increased micronutrient status, reduction of anaemia prevalence and improved growth in most settings [22,23]. However, in some settings simultaneous prevention of common diseases (e.g. malaria, other infectious diseases) might be needed to see an effect as some studies in malaria-endemic areas using fortified products have demonstrated limited efficacy [24-26].

Nutrition-sensitive interventions such as providing oral rehydration salts (ORS) and zinc supplements for the treatment of acute diarrhoea in young children and preventive anthelminthic treatment to pregnant women in endemic areas are recommended by WHO [7,13,14]. A recent Cochrane review concludes that in areas where the prevalence of zinc deficiency and malnutrition is high, children older than 6 months are likely to benefit from zinc supplementation by shortening the duration of acute diarrhoea [27]. Although a recently published Cochrane review including 4 RCTs did not show an effect of albendazole on maternal anaemia or preterm birth or perinatal mortality (not reporting on any other antenatal care outcomes) [28], the 2017 WHO Guidelines on preventive chemotherapy to control soil-transmitted helminth infections in high-risk groups [29], keep the recommendation of preventive treatment as it helps lessen the burden of other infections and contributes to a sustained reduction of transmission. Other nutrition-sensitive interventions include WASH related interventions, such as providing soap and chlorine to households. A recent meta-analysis has found that soap use or availability or the use of treated water was significantly associated with lower infection with any soil-transmitted helminths [30]. Further, a systematic review [31], multi-country reviews [32], and a pooled analysis of several studies [33] as well as a recent analysis in Ethiopia [34] show a decreased risk of diarrhea following hand washing promotion interventions. The effect of nutrition-sensitive interventions alone on malnutrition (stunting or wasting) has not been demonstrated with clear evidence yet, but such interventions might be the key for success in an integrated programme that additionally includes nutrition-specific and agricultural interventions.

In the past, mainly studies either focusing on agriculture interventions alone, nutrition-specific interventions alone (supplementation and food fortification), and nutrition-sensitive interventions alone (improvement of WASH conditions or treatment of infectious diseases) have been conducted and some of them have shown limited effects. Combining the three types of interventions is promising and may result in a larger success rate, as different areas that influence growth are included.

Thus, the research questions for the two suggested studies are:

Study 1: Can linear growth in children during their first 24 months of life be enhanced after the provision of agricultural services, nutritionally enhanced and WASH products as well as nutrition and WASH training over the period of the 1000 days window of opportunity (from conception until the child's 2nd birthday) when compared to the control group provided only with agricultural services?

Study 2: Can the rate of linear growth in children between 6-59 months of age be enhanced after the provision of agricultural services, nutritionally enhanced and WASH products, diversified crops as well as nutrition and WASH training over the period of 2 years when compared to the control group provided only with agricultural services?

4. RESEARCH OBJECTIVES

4.1 Overall Objective

The purpose of the studies is to assess the programme effectiveness of an integrated approach (agriculture, nutrition-specific and nutrition-sensitive) compared to an agricultural approach alone and its impact on nutritional outcomes for mothers and young children as well as to identify and assess the conceptual and operational factors at the different stages of the intervention package that may have affected these outcomes.

4.2 Primary Objective

Study 1 seeks to assess the effect of the integrated intervention package on growth, birth outcomes, anaemia, micronutrient deficiencies, and morbidity in mothers and their offspring in comparison to the control arm; thereby attributing changes in dietary and hygiene patterns to such effects.

Study 2 seeks to determine the effect of the integrated intervention on growth, anaemia, dietary diversity, young child feeding and WASH patterns in comparison to the control group and access to and coverage of diversified crops and nutrition products.

4.3 Secondary Objectives

Secondary objectives of study 1 and study 2 are to identify and assess the conceptual and operational factors at the different stages of the intervention package that may have affected the outcome and to determine unintended consequences of the interventions.

4.4 'Safety' Objectives

Studies 1 and 2 seek to assess the inappropriate use of nutritionally adequate products in the intervention groups. Specifically, the studies investigate if in the intervention group as compared to the control group:

- a lower proportion of the children less than 6 months of age are exclusively breastfed
- complementary food is introduced too early
- dietary diversity is lower in pregnant/lactating women and children
- there is an increase of overweight and obesity in pregnant/lactating women and children
- there is an increase of morbidity incidences such as diarrhoea in the children (this is monitored monthly in study 1 and quarterly in study 2)

5. CONCEPTUAL FRAMEWORK AND OPERATIONALIZATION

Figure 1 shows how project activities (inputs) will lead to outputs and result in outcomes as well as the potential impact of the planned activities. The model shows the combined activities planned within study 1 and study 2.

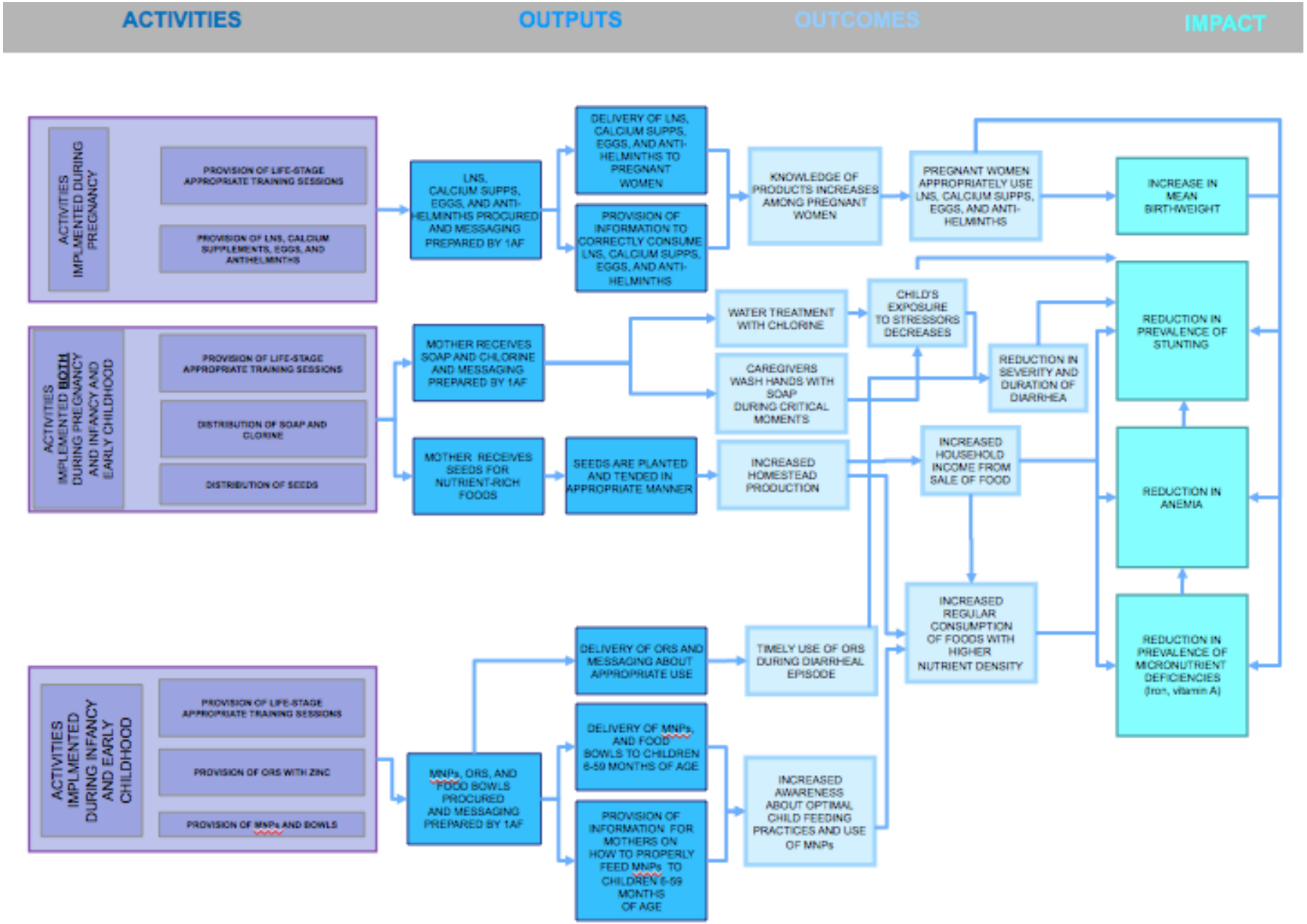


Figure 1: Logic model for the CIFF/1AF programme that includes the two studies presented in this protocol

The objectives of the programme intervention and the indicators to assess achievement of these objectives are shown in Table 1.

Table 1: Objectives and corresponding key indicators

Level of data	Hypothesis	Indicators	Proposed studies
Purpose 1: To assess the effect of the 1AF intervention package on birth outcomes, anemia, micronutrient deficiencies, stunting, and morbidity in mothers and their young children			
Impact	Decreased stunting in children receiving the intervention package (or parts thereof)	• Change in length-for-age z scores (LAZ) • Percentage of children whose LAZ is below -2 standard deviations from the median of the WHO Child Growth Standard	• Studiy 1&2
Impact	Reduced prevalence of anemia and micronutrient deficiencies in children receiving the intervention package	• Change in proportion with anaemia • Change in haemoglobin concentration • Change in retinol binding protein concentration (i.e. vitamin A status) • Change in concentration of serum ferritin and soluble transferrin receptor (i.e. iron status)	• Study 1
Impact	Increased birth weight of children from mothers having received the intervention package during the pregnancy	• Change in birth weight	• Study 1
Outcome	Reduced prevalence (or incidence) in diarrheal disease in infants and young children receiving the intervention package	• Age- and sex-specific morbidity rates with a focus on diarrhoea	• Study 1
Purpose 2: To identify and assess the conceptual and operational factors at the different stages of the intervention package that may have affected the outcome			
Outcome	Increased intake of nutritional products among pregnant and lactating women and children	• Consumption of adequately formulated nutritional products in the period preceding data collection • Monitoring of type, frequency and quantity of adequate nutritional products	• Study 1&2
Outcome	Increased dietary diversity among pregnant and lactating women	• FANTA/FAO minimum Dietary Diversity-Women	• Study 1
Outcome	Increased adherence to adequate child feeding practices	• Prevalence of early initiation of breastfeeding • Prevalence of exclusive breastfeeding • Duration of exclusive breastfeeding • WHO suite of IYCF (Infant and Young Child Feeding) indicators of dietary diversity, frequency, and adequacy	• Study 1 • Study 1&2
Outcome	Improved WASH practices	• Ability to identify five critical times for handwashing • Proportion of households with soap and water available	• Study 1&2
Outcome	Improved access to and availability of nutritionally adequate products for pregnant and lactating women and children	• Access to nutritionally adequate foods • Affordability of such products as a function of the socio-economic status of the respondent	• Study 1&2

Output	Increased knowledge and awareness of the importance of adequate antenatal and child feeding practices and care	• Ability to differentiate between facts and myths on antenatal and child feeding practices and care • Knowledge of new information gathered on child feeding practices and formulated nutritional products for pregnant and lactating women and children • Knowledge of the risks for not having adequate antenatal and child feeding practices and care • Awareness of sources of information for antenatal and child feeding practices	• Study 1&2
Purpose 3: To determine unintended consequences of the interventions			
Outcome	Inappropriate use of nutritionally adequate products	• Percentage of children less than 6 months of age not exclusively breastfed due to provision of complementary foods before 6 months of age	• Study 1&2
Impact	Increase in the prevalence of overweight and obesity	• Percentage increase in the proportion of children whose WHZ (weight for height z-score) is above +2 and +3 standard deviations from the median of the WHO Child Growth Standard	• Study 1&2

Several factors may influence our results, which we will take into account during data analysis. The following parameters assessed at baseline have been defined as independent variables to potentially influence the outcome at delivery and study end of **study 1**:

- maternal height
- maternal BMI (body mass index)
- maternal age
- maternal education
- gestational age at enrolment
- parity
- time interval from prior birth
- household socio-economic status
- household food insecurity
- site

The following additional parameters assessed at round 3 (delivery) have been defined as independent variables for study endpoint outcomes:

- child sex
- mode of delivery

The following parameters assessed at baseline have been defined as independent variables to potentially influence the outcome at round 2 and 3 of **study 2**:

- maternal age
- maternal education
- parity
- time interval from prior birth
- child sex
- household socio-economic status
- household food insecurity
- whether cluster received health insurance (other study taking place in the same district)
- site

6. HYPOTHESIS/RESEARCH QUESTIONS

Study 1 hypothesis: Linear growth in children during their first 24 months of life will improve after the provision of agricultural services, nutritionally enhanced and WASH products as well as nutrition and WASH training over the period of the 1,000 days window of opportunity when compared to the control group provided only with agricultural services.

Study 2 hypothesis: Linear growth in children between 6-59 months of age will improve after the provision of agricultural services, nutritionally enhanced and WASH products and diversified crops as well as nutrition and WASH training over the period of 2 years when compared to the control group provided only with agricultural services.

Table 2 below indicates the expected direction of relationship between the independent variables and the primary outcome (length at 24 mo of age in study 1 and length after 2 years of intervention in study 2).

Table 2: Expected direction of relationship between independent variables and primary outcome (linear growth)

Independent variable	Direction of relationship	Study
Maternal height	Positive	1
Maternal BMI	Positive unless overweight/obese	1
Maternal age	Negative in youngest as rather inexperienced and physiologically less ready	1&2
Maternal education	Positive	1&2
Gestational age at enrolment	Younger gestational age is positive as duration of intervention is longer	1
Parity	Negative (multiparous higher risk of stunting)	1&2
Time interval from prior birth	Longer interval is positive	1&2
Household socio-economic status	Positive	1&2
Household food insecurity	Negative	1&2
Health insurance intervention	Positive if people go more often to health centres	2
Site	Direction is not clear	1&2
Child sex	Positive with female sex	1&2
Mode of delivery	Caesarean section negative	1

7. STUDY DESIGN AND SAMPLING STRATEGY

7.1 Study design and sampling procedures

Study 1:
General study design: Study 1 is a cluster-randomized, parallel-group, prospective, follow-up effectiveness study over a period of 1000 days comparing 2 groups:

a) Intervention group: **Pregnant women** will be given LNS (1 sachet/day), raw eggs (2/day), and an anthelminthic drug (albendazole) in the second trimester of pregnancy, as well as soap and chlorine solution for the woman and the household. After delivery these products will be continued until the child reaches 6 months of age. Thereafter, LNS and eggs for mothers and anthelmintic drugs will be discontinued and instead, the **child** will receive LNS (1 sachet/day), one egg/day and Oral Rehydration Salts (ORS) along with zinc tablets (20 mg/day) for treatment in case of acute diarrhoea. These products will be given until the child reaches 2 years of age. The products will be accompanied by life stage-appropriate nutrition and WASH trainings (pregnancy, lactation, infant and young child feeding), as well as SMS reminders to highlight certain messages on antenatal care and nutrition. All products and trainings will be

provided free of charge. The households in the intervention group will also have the same agricultural intervention as the control group.

b) Control group: All households will be provided with agricultural training (every 2 weeks on average) for free. In addition, households can also enrol for the following products on credit: compost booster, cook stoves, seeds (onions, maize, indigenous greens, beans), maize storage bags, drying tarps, trees, solar lights, fertilizer, actellic dust (insecticide), re-usable sanitary pads.

We anticipate recruiting 1200 (600 in each group) pregnant women into the study (see section 7.2 for sample size calculation); this is expected to yield a sufficiently large sample of children later in the study. Women will be recruited from 120 clusters (randomly assigned to intervention or control) that will be drawn from from Kimilili and Webuye districts in Bungoma County in Western Province of Kenya.

We anticipate recruiting 1,200 (600 in each group) pregnant women into the study (see section 11.2 for sample size calculation); this is expected to yield a sufficiently large sample of children later in the study. Women will be recruited from 120 clusters (randomly assigned to intervention or control) that will be drawn from from Kimilili and Webuye districts in Bungoma County in Western Province of Kenya.

The communities will be informed about the study in village meetings by CHVs and by conducting outreach within their catchment area to identify pregnant women. Pregnant women will then be screened by 1AF enumerators. During **screening**, a few questions on health status and pregnancy will be asked. If the woman is prior or equal to 20 weeks of gestation (according to last menstrual period), has no visible severe disease and no allergy to peanuts or milk products, and confirms anticipated residence in the area for the coming 30 months, written informed consent for her and her offspring will be sought from her. She will then be asked to provide a urine sample to confirm pregnancy and she will be enrolled if pregnancy is confirmed. Following the screening, 5 assessment rounds (baseline and 4 follow-up assessments during the intervention) will be conducted at the participant's homes (rounds 1-3) or at a central place (rounds 4 and 5) within walking distance from their homes (Figure 2). Assessment round 3 (immediately) after delivery will be conducted as home visits or clinic visits in case of delivery at a clinic. Details of assessment procedures for each round are illustrated in (Figure 3).

Round 1 (Enrolment, ≤20 wk of gestation)**:**
On the day of enrolment the round 1 assessment will be done. As part of this, the following information will be collected: household demographics and characteristics, maternal education; knowledge, attitude and practices (KAP) of specific dietary and nutrition practices during pregnancy; individual dietary diversity; antenatal care; WASH practices; height, weight and mid-upper arm circumference; maternal haemoglobin concentration and malaria parasitaemia from a capillary blood sample. After round 1, participants randomly allocated to the intervention group will start receiving the intervention package.

Round 2 (Gestational age of 34±1 wk)**:**
In round 2, interview questions related to diet and nutrition KAP during pregnancy, dietary diversity, antenatal care, and WASH will be asked. Additionally, MUAC (mid-upper arm circumference) will be measured and a capillary blood sample for measurement of haemoglobin concentration, malaria parasitaemia and micronutrient status will be provided.

Round 3 (Within 24-48 hours after delivery)**:**
The mother-child pair will be visited within 24-48 hours after delivery. The following information will be recorded: delivery date and time, delivery method, recent antenatal care, and early initiation of breastfeeding. The mother will be assessed for MUAC but no blood sampling will be conducted. For the newborn, head circumference, birth weight and birth length, and haemoglobin concentration (from a heelprick) will be measured.

Round 4 (At 6.5 mo ± 1 mo of age of offspring)**:**
This assessment will be conducted when the child turns 6.5 months old. Breastfeeding and other infant and young child feeding indicators, child morbidity, maternal dietary diversity, postnatal care, and WASH information will be gathered. In mothers, MUAC and weight will be measured and haemoglobin concentration and malaria parasitaemia from a capillary sample will be assessed. In

children, length, weight and head circumference will be measured and a capillary blood sample for haemoglobin concentration, malaria parasitaemia and micronutrient status will be provided.

Round 5 (At 24 ± 1mo of age of offspring)**:**
This assessment will be conducted when the child turns 24 months old. Questionnaire-based information on child feeding, child dietary diversity, child morbidity and WASH will be collected. As in round 4, child length, weight and head circumference will be measured and a fingerprick blood sample will be provided for the measurement of haemoglobin concentration, malaria parasitaemia, and micronutrient status. No maternal biomarkers will be collected at this point.

As part of the monthly visits to the participants' households, the CHV will also collect data on intervention adherence and recent morbidity.

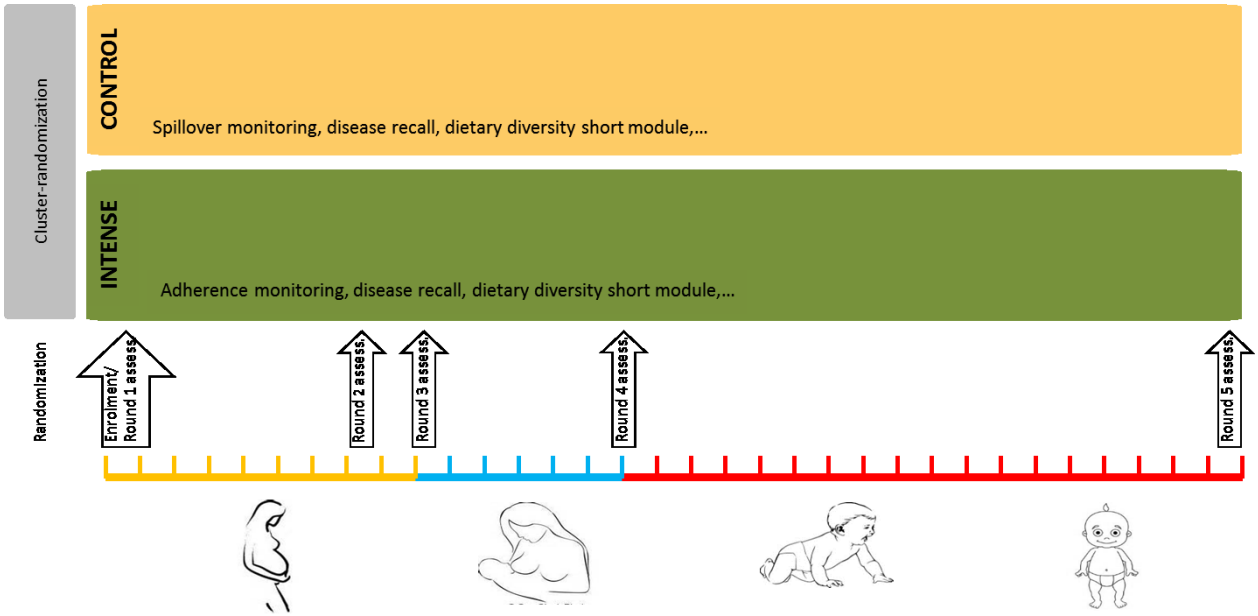


Figure 2: Timing of assessment rounds for study 1.

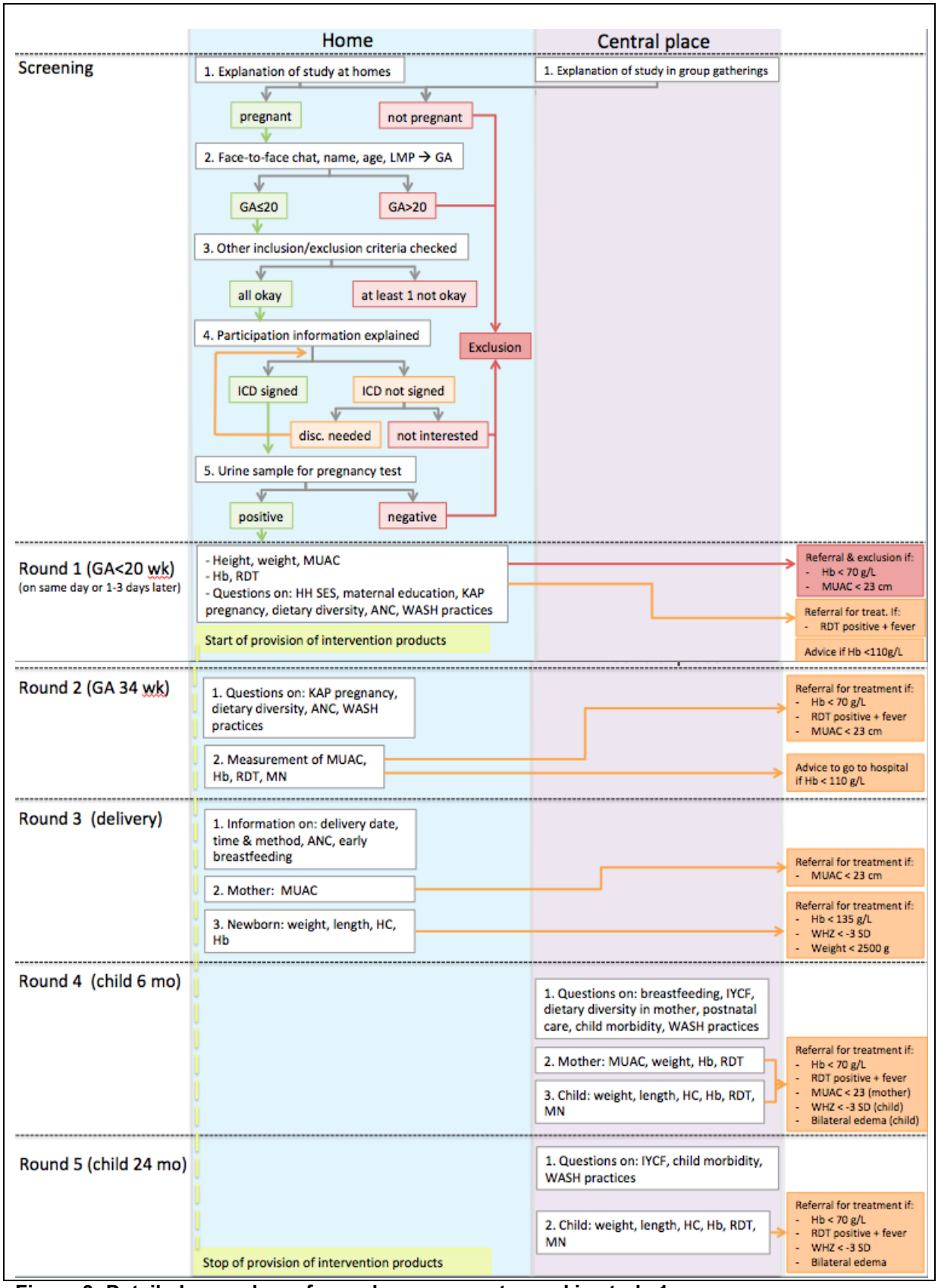


Figure 3: Detailed procedures for each assessment round in study 1

(LMP: last menstrual period; GA: gestational age; ICD: informed consent document; MUAC: mid-upper arm circumference; Hb: haemoglobin; RDT: rapid diagnostic test (for malaria); HH: household; SES: socioeconomic status; KAP: knowledge, attitude and practice; ANC: antenatal care; WASH: water, sanitation and hygiene; MN: micronutrients; HC: head circumference; IYCF: infant and young child feeding)

The detailed procedures of study 1 are summarized in Table 3 below.

Table 3: Study 1 summary table of procedures and assessments

Study Periods	Screening	Intervention Period				
Visit/Round	0	1	2	3	4	5
Time (hour, day, week)	≤20 wk GA	≤20 wk GA	34±1wk GA	Delivery +48h	Infant 6.5±1 mo old	Infant 24±1 mo old
Randomisation of clusters (done prior to recruitment)						
Oral consent for screening questions	x					
Pregnancy and health status questions	x					
In- /exclusion criteria	x					
Written participant information and informed consent		x				
Pregnancy test		x				
Re-assessment of in-/exclusion criteria		x				
Household demographics/characteristics		x				
Maternal education		x				
Maternal anthropometry		x	x	x	x	
Child anthropometry				x	x	x
Capillary blood sampling in women		x	x		x	
Capillary blood sampling in children				x	x	x
Ante-/postnatal care		x	x	x	x	
Dietary and nutrition practices KAP, dietary diversity (pregnancy, lactation)		x	x		x	
WASH practices		x	x		x	x
Delivery information (incl. breastfeeding, birth weight and length)				x		
Breastfeeding and other IYCF indicators					x	x
Child dietary diversity					x	x
Child morbidity					x	x
Intervention adherence			x	x	x	x

Study 2:
General study design: Study 2 is a cluster-randomized, parallel-group, prospective, follow-up effectiveness study over a period of 2 years comparing 2 groups of children 6-35 months of age at recruitment:

a) Intervention group: All selected households with children 6-35 months of age at recruitment will receive MNP (1 sachet every three days per child) and ORS along with zinc (20 mg/day) for treatment of acute diarrhoea. The households will also be provided with soap, chlorine solution, poultry (8 chickens at start of intervention), and seeds for red onion and indigenous greens (March 2018 and March 2019). The products will be accompanied by monthly nutrition and WASH trainings. The products and trainings will be provided free of charge. Additionally, all households will receive the agricultural package as in the control group.
b) Control group: All households will be provided with agricultural training (every 2 weeks on

average) for free. In addition, households can also enrol for the following products on credit: compost booster, cook stoves, seeds (onions, maize, indigenous greens, beans), maize storage bags, drying tarps, trees, solar lights, fertilizer, actellic dust (insecticide), re-usable sanitary pads.

We anticipate recruiting 2,000 (1,000 in each group) children 6-35 months of age into the study (see section 7.2 for sample size calculation). Children will be recruited from 100 clusters (randomly assigned to intervention or control) that will be drawn from Lugari district in Kakamega County located in the Western Province of Kenya.

Questionnaire based and anthropometric data will be collected in **3 rounds** at a central place in walking distance from participant's homes one year apart from each other (Table 4). The following information will be collected in **round 1** (baseline assessment prior to the actual start of intervention distribution):

- Age
- Height and weight
- Household demographics/characteristics and caregiver's education
- Dietary diversity, breastfeeding and infant and young children feeding (IYCF) practices
- WASH practices
- Child morbidity

In **rounds 2 and 3,** information on dietary diversity, breastfeeding and IYCF practices, WASH practices and child morbidity will be collected again. Additionally, changes in adherence and coverage of the intervention package as well as unintended outcomes (e.g. reduction of exclusive breastfeeding due to premature introduction of complementary foods) will be assessed.

Table 4: Study 2 summary table of procedures and assessments

Study Periods	Intervention Period		
Visit/Round	1	2	3
Time (hour, day, week)	Prior to start of intervention	1 year after start of intervention	2 years after start of intervention
Age (Date of birth)	x		
Anthropometry	x	x	x
Household demographics/characteristics	x		
Mother's/caregiver's education	x		
Dietary diversity, breastfeeding and child feeding practices	x	x	x
WASH practices	x	x	x
Child morbidity	x	x	x
Adherence to and coverage of intervention package		x	x

7.2 Sample size and randomization

Study 1 and 2:

Some indicators included in study 1, such as maternal haemoglobin, child haemoglobin, and child length-for-age z score (LAZ), are measured more than once in the same study subject over time. This is also the case for haemoglobin and height-for-age z score (HAZ) in the children in study 2. For these indicators, the average change in outcomes in study subjects in the intervention group will be compared to the average change in study subjects in the control group. Other indicators in study 1, such as birth weight and length, are measured only once in each study subject. For these indicators, the average value in the intervention group will be compared to the average value in the control group.

The sample size depends on the size of the desired minimum difference between the intervention group and the control group, which can be detectable with statistical significance. This minimum

difference is expressed as the effect size, which is the difference in the value of the indicator between the two groups to be compared divided by the standard deviation of the indicator. For those outcomes measured more than once, the indicator is the change over time in study subjects. This effect size can be written as follows:

$$\frac{\left[\text{Mean}\left(LAZ_{Cx} - LAZ_{Cy}\right)_{\text{Group1}} - \text{Mean}\left(LAZ_{Cx} - LAZ_{Cy}\right)_{\text{Group2}}\right]}{\text{Standard deviation}\left(LAZ_{Cx} - LAZ_{Cy}\right)_{\text{Group1}}}$$

Where C_x and C_y stand for the two measurements of those indicators which are measured twice.

The sample size calculations make the following assumptions: 1) a two-tailed comparison (that is, there is no *a priori* conclusion about which group is higher and which is lower), 2) statistical significance is defined as a p value less than 0.05, 3) the power of the study is at least 0.8, and 4) that the standard deviation of the indicator in both study groups is the same.

Although it is difficult to find highly comparable interventions and their effect sizes for key outcomes put forth, Table 5 below provides an overview of observed effect sizes for somewhat similar interventions and outcomes.

Table 5: Effect sizes in children for similar outcomes and interventions reported in the literature

Description of intervention	Reported outcome	Effect size (95%CI)	Reference
Maternal education on complementary feeding and provision of complementary foods	Weight gain	0.34 (0.11, 0.56)	[35]
	Linear growth	0.26 (0.08, 0.43)	
Maternal education on complementary feeding alone	Weight gain	0.30 (0.05, 0.54)	
	Linear growth	0.21 (0.01, 0.41)	
Micronutrient powders	Haemoglobin	0.98 (0.55, 1.40) 0.69 (0.07, 1.32) 0.33 (0.87, 1.53) 0.20 (-1.24, 1.64)	[36-40]
	LAZ	0.04 (-0.13, 0.22)	
	Serum retinol	1.66 (-1.60, 4.92)	
	Serum ferritin	1.78 (-0.31, 3.88)	
Lipid-based nutrient supplements (children)	Haemoglobin	0.63 (-0.48, 1.73) 0.52 (1.84, 2.88)	[41-43]
	Linear growth	0.22 (0.05, 0.39)	
	Weight gain	0.25 (0.19, 0.31)	
Lipid-based nutrient supplements (pregnancy&infancy)	Linear growth	0.28 (0.07, 0.50)	[44]
	Weight gain	0.24 (0.15, 0.33)	
Education on IYCF (programmes)	Linear growth	0.12 to 0.64	[45]
	Weight gain	-0.06 to 0.96	
Complementary foods and education on IYCF (programmes)	Linear growth	0.0 to 0.14	
	Weight gain	0.18 to 0.24	
Iron fortification (infants, pre-school and school-children)	Haemoglobin	0.55 (0.34, 0.76)	[37,46]
	Serum ferritin	0.91 (0.38, 1.44)	
Vitamin A fortification	Serum retinol	0.61 (0.39, 0.83)	

For study 1, considering field logistics (number of pregnant women that can be recruited within 3 months in a manageable area) the number of pregnant women that is estimated to be available for recruitment into the study is 1,200. The primary outcome is change in length-for-age z-score (LAZ) in the children of enrolled women between birth and the end of follow up at 24 months of age. The effect size that is detectable takes into account the design effect of cluster randomization (design effect = 1.3) which is based on the design effect found in other studies and study subject refusal and loss to follow up. For the latter, it was assumed that 95% of eligible pregnant women would consent to participation and that 80% of enrolled women would complete follow-up at delivery. Of children born to women completing follow-up, 95% would be recruited for continued follow-up, and 75% of enrolled

children would still be enrolled at final data collection at 24 months of age. Taking into account all these assumptions for the recruitment of a total of 1,200 pregnant women (600 women in the control and 600 women in the intervention group) in 120 clusters this will allow detecting an effect size of 0.26 in LAZ in children between 6-24 months of age, which is a reasonable effect size when compared to another study in which LNS was used during pregnancy and infancy (Table 5). Effect sizes for changes in haemoglobin concentration in children, one of the secondary outcomes in our study, are higher than for linear growth and thus our sample size will allow detecting changes in this indicator (Table 5).

Sample size was also calculated for birth weight. From prior studies of birth weight in less-developed countries, an average birth weight in the study population of 3,000 g, a standard deviation of 500 g, and a birth weight 85 g larger in the intervention population was assumed. Furthermore, it was assumed that the study drop out will be at 20%. A sample size of about 1,090 women is needed, or 545 per study arm which is covered with the calculation for the primary outcome with 600 women per arm.

For study 2, considering logistical challenges we estimated that a maximum of 2,000 children 6-35 months of age could be recruited. The primary outcome is change in length-for-age z-score (LAZ) between enrolment and after 2 years of follow up. The effect size that is detectable takes into account the design effect of cluster randomization (design effect = 1.3) as in study 1 and assumes that caregivers of 95% of eligible children would consent to participation and that 80% of enrolled children would complete the 2 years follow-up. Taking into account all these assumptions for the recruitment of a total of 2,000 children (1,000 children in the control and 1,000 children in the intervention group) in 100 clusters this will allow detecting an effect size of 0.17 in LAZ or HAZ in children between baseline and 2 years follow up, which is a reasonable effect size and has been shown in other studies before (Table 5). As in study 1, our sample size will allow detection of changes in haemoglobin concentration as effect sizes are higher than for linear growth (Table 5).

As these are cluster-randomized studies, no individual randomization will take place. Clusters will be created according to village size and location with the aim to create clusters that correspond with village(s) boundaries and are big enough to likely have 10 pregnant women to be recruited in study 1, and 20 children in study 2. The clusters will be comprised of villages that are geographically close to one another and separate from other clusters. Once the clusters are determined, they will be randomly assigned to control or treatment in both studies.

7.3 Study population

7.3.1 Eligibility criteria

Participants fulfilling all of the following **inclusion** criteria are eligible for the study:
Study 1:

- Pregnant women (≥ 18 years of age) with gestational age ≤20 weeks
- Written Informed Consent as documented by signature

Study 2:

- Children 6-35 months of age at recruitment
- Written Informed Consent as documented by signature

The presence of any one of the following **exclusion** criteria will lead to exclusion of the participant
Study 1:

- Family does not intend to stay within the study area for at least the following 30 months
- Known history of allergy towards peanut or milk products
- Visible severe disease

Study 2:

- Family does not intend to stay within the study area for at least the following 24 months

- Visible severe disease

7.3.2 Recruitment and screening

Study 1:
During community meetings and outreach CHVs will inform and 1AF field officers will screen potential participants. In case a woman declares to be pregnant, oral consent for a screening assessment including providing the date of last menstrual period and checking for inclusion/exclusion criteria will be taken. If woman is eligible written informed consent will be sought and the woman will be asked to provide a urine sample for a pregnancy test. Women will be enrolled in case pregnancy is confirmed. All pregnant women meeting all the inclusion/exclusion criteria will be included in the study until the anticipated sample size in each selected cluster is reached.

Study 2:
Household lists of farmers participating in the 1AF programme will be used to determine whether a household has at least one eligible child between 6-35 months of age. A child will be included once inclusion and exclusion criteria have been checked and written informed consent is obtained from the caregiver. The baseline assessment will then be conducted. 1AF field officers will be responsible for recruiting the selected children.

7.3.3 Criteria for withdrawal/discontinuation of participants

Study 1:
Pregnant women are free to withdraw themselves or their children from participation in the study at any time. If the pregnant woman is being diagnosed with severe anaemia (haemoglobin (Hb)<70g/L) or severe acute malnutrition (MUAC < 23 cm) at round 1, she will be excluded from participation and will be referred for treatment according to national guidelines to the nearest health centre. If the pregnant woman is being diagnosed with malaria parasitaemia and has an axillary temperature of >37.5°C in round 1, she will be referred for treatment but will continue participating in the study after temporary suspension from interventions if required as assessed by the study physician. If the pregnant woman has an Hb between 70 and 109 g/L in rounds 1 or 2, she will be advised by the study team to go to the hospital for further management. This will be facilitated by CHVs. If the mother, infant or child is being diagnosed with malaria parasitaemia and an axillary temperature of >37.5°C, or severe anaemia (Hb<70g/L), or they suffer from severe acute malnutrition (WHZ<-3 and/or bilateral oedema for child, MUAC < 23 cm for mother) in rounds 2 to 5, affected participants will be referred for treatment according to national guidelines but will continue in the study after temporary suspension from interventions if required as assessed by the study physician. If a child is born with low birth weight (<2500 g) and/or has a Hb < 135 g/L, he/she will be referred for a medical check. Further, study participants will be discontinued from participation in the study in case of any clinical significant adverse event (AE), or any other medical condition or situation that prevents continued participation in the study. If a participant is discontinued no specific follow-up assessments will be conducted other than the follow up until resolution in case of exclusion due to a serious adverse event (SAE). Participants will not be replaced, as a non-consent and dropout rate of 46% prior to reaching 24 months of age is included in the sample size calculation.

Study 2:
Caregivers are free to withdraw their children from participation in the study at any time. If a child is being diagnosed with severe acute malnutrition (WHZ<-3 and/or bilateral oedema) at round 1, he/she will be excluded from participation and will be referred for treatment according to national guidelines to the nearest health centre. If a child suffers from severe acute malnutrition (WHZ<-3 and/or bilateral oedema) in rounds 2 and 3, affected participants will be referred for treatment according to national guidelines but will continue in the study after temporary suspension from interventions if required as assessed by the study physician. Further, study participants will be discontinued from participation in the study in case of any clinical significant adverse event (AE), or any other medical condition or situation that prevents continued participation in the study. If a participant is discontinued no specific follow-up assessments will be conducted other than the follow up until resolution in case of exclusion due to a serious adverse event. Participants will not be replaced, as a non-consent and dropout rate of 24% prior to the final assessment after 2 years is included in the sample size calculation.

7.4 Interventions

LNS (Enov' Mum) (to be provided to pregnant women and up to 6 months after delivery in intervention group in study 1)

Enov` Mum has been designed based on recommendations of WHO, World Food Programme (WFP) and UNICEF [11] and is produced by Nutriset. This lipid-based Ready-to-Use Food supplement for home fortification aims at improving the nutrition and health status of pregnant and lactating women by filling micronutrients gaps in a non-emergency context thereby improving the development of the foetus and the infant. Enov'Mum is composed of the following ingredients: vegetable oils (rapeseed, palm, soy) skimmed milk powder, sugar, whey powder, peanuts, soy isolate, maltodextrin (corn), stabilizer (fully hydrogenated vegetable fat, mono- and diglycerides), vitamin and mineral complex, and aroma. This product does not contain any genetically modified organism and does not contain any ingredients of animal origin, except dairy products. Enov'Mum will be provided in individual 20 g sachets (**Figure 4**) and pregnant and lactating women will consume one sachet per day containing essential fatty acids and one to two recommended daily allowances (RDA) of vitamins and minerals (**Table 6**).

As adherence to antenatal iron/folic acid supplementation in Kenya is low (with 30.1% receiving no iron at all during pregnancy, 65% receiving any, but of those 53% receiving it for less than 60 days) [3] supplementing the women with LNS additionally is not expected to have any negative effects, and WHO guidelines during emergencies even state that iron/folic acid supplementation does not need to be discontinued while multiple micronutrient supplements are provided [11]. The participating pregnant women will remain under the national antenatal care services and will be encouraged to attend those in the same way as non-study participants are.

Table 6: Composition of Enov'Mum per 20 g sachet

Nutrient	Unit	20 g LNS portion
Energy	kcal	120
Protein	g	2.6
Lipids	g	9.2
Linoleic acid	g	1.58
α-Linolenic acid	g	0.65
Vitamin A, RAE	mg	800
Thiamin (B1)	mg	1.4
Riboflavin (B2)	mg	1.4
Pyridoxine (B6)	mg	1.9
Cobalamine (B12)	µg	2.6
Folate, DFE	µg	600
Vitamin C	mg	55
Vitamin D	µg	15
Vitamin E	mg	15
Calcium	mg	60
Copper	mg	1.15
Iodine	µg	250
Iron	mg	20
Magnesium	mg	9
Phosphorus	mg	57
Potassium	mg	104
Selenium	µg	30
Zinc	mg	10

Figure 4: LNS Enov'Mum (daily portion)

Anthelminthic treatment (to be provided to pregnant women in intervention group once during the second trimester)
A single dose of 400 mg albendazole will be provided to all pregnant women in the intervention group during the second trimester (13-27 weeks of gestation).

LNS (Enov' Nutributter) (to be provided to children 6-24 months of age in intervention group in study 1)
Enov'Nutributter is a lipid based nutrient supplement produced by Nutriset and designed to promote infant growth, motor development and to prevent malnutrition in children 6-24 months of age. Its micronutrient content is especially calculated to meet the needs of a child in this age group (see Table 7 for the composition). Enov'Nutributter is a paste based on peanuts, sugar, vegetable fat, skimmed milk powder, maltodextrin and whey, enriched with a vitamin and mineral complex and can either be consumed directly or added to the complementary food. Enov'Nutributter will be provided in individual 20 g sachets (Figure 5) and caregivers will be instructed to feed one sachet per day..

Table 7: Composition of Enov'Nutributter per 20 g sachet

Nutrient	Unit	20 g LNS portion
Energy	kcal	107
Protein	g	2.6
Lipids	g	6.9
Linoleic acid	g	1.15
α-Linolenic acid	g	0.27
Calcium	mg	60
Phosphorus	mg	86
Potassium	mg	152
Magnesium	mg	16
Zinc	mg	4
Copper	mg	0.2
Iodine	µg	250
Iron	mg	9
Iodine	µg	90
Selenium	µg	10
Vitamin A, RAE	mg	400
Vitamin C	mg	30
Thiamin (B1)	mg	0.3
Riboflavin (B2)	mg	0.4
Pyridoxine (B6)	mg	0.3
Cobalamine (B12)	µg	0.5
Folic acid	µg	80
Pantothenic acid	mg	1.8
Niacin	mg	4
Sodium	mg	<58

Figure 5: LNS Enov'Nutributter (daily portion)

MNP (MixMe) (to be provided to children 6-59 months of age in intervention group in study 2)
The MNP (MixMe^{TM}) to be used is produced by the company DSM according to recommendations by WHO [12] and distributed by UNICEF and WFP with the aim to improve diet quality of nutritionally vulnerable groups, such as young children [47]. MNPs are dosed into sachets (Figure 6) containing the dry powder with micronutrients that can be added to any semi-solid or solid food that is ready for consumption.
MNP will be provided in individual 1g sachets, which consist of the micronutrients as in Table 8. Children will consume 1 sachet every three days (120 days/year).

Table 8: Vitamin and mineral content in a 1 g sachet of MNP

Nutrient	Unit	MNP (1g portion)
Vitamin A, RAE	mg	400
Thiamin (B1)	mg	0.1
Riboflavin (B2)	mg	0.5
Niacin (B3)	mg	6
Pyridoxine (B6)	mg	0.5
Cobalamine (B12)	µg	0.9
Folate, DFE	µg	150
Vitamin C	mg	30
Vitamin D	µg	5
Vitamin E	mg	5
Copper	mg	0.56
Iodine	µg	90
Iron	mg	10
Selenium	µg	17
Zinc	mg	4.1

Figure 6: 1g sachet of MNP (to be consumed every three days)

Oral Rehydration Salts (ORS) and zinc (to be provided to offspring from 6 to 24 months of age in intervention group in study 1 and children 6-59 months of age in intervention group in study 2 in case of acute diarrhoea)

Single dose packages of ORS and 20 mg zinc dispersible tablets will be provided to the mothers in the intervention group when the offspring turns 6 months old in study 1 and to all intervention households with recruited children in study 2. Mothers and caregivers will be taught on how to treat dehydration at home according to the recommendations of the Kenya National Formulary for Primary Care Level 2008 and of the WHO [48]. They will be instructed to contact their CHV if the child shows signs of dehydration or still symptomatic after 7 days. This will allow the CHV to refer the child to a clinic if needed. Mothers and caregivers will be given 14 zinc supplements (one 20 mg tablet daily for 14 days) and 21 ORS sachets (10.3 g/sachet), which is enough ORS to treat the child for approximately 7 days. Mothers will be instructed to give 50-100 mL of ORS after each loose stool for children 6-23 months of age (studies 1 and 2) and 100-200 mL after each loose stool for children > 23 months of age (study 2). Additionally, the mothers and caregivers will be trained to administer one tablet of dispersible zinc daily for 14 days, which will shorten the current episode but will also prevent near future episodes. During regular visits by CHVs the used courses will be replaced.
Individual sachets of DawaLyte ORS each containing 10.3 g and composed of anhydrous glucose, potassium chloride, sodium chloride and trisodium citrate) will be used in the study (Figure 7). JuniorZinc in the form of dispersible tablets (20 mg zinc as zinc sulphate per tablet) will be used in the study (Figure 8). Both products will be supplied by Dawa Ltd.

Figure 7: ORS sachets to be distributed in study 1 and study 2

Figure 8: Zinc dispersible tablets to be used in study 1 and 2

Chlorine solution (to all intervention households during the whole intervention period in both studies)
Chlorine solutions will be distributed in 500 mL bottles (Aquaguard supplied by Supersleek Ltd.) once per year and mothers/caregivers will be trained on how to properly use it.

Soap (to all intervention households during the whole intervention period in both studies)
One 600 g bar of local soap will be provided per household per month.

Raw eggs (to all intervention households in study 1)
Raw eggs will be provided to the households during the whole duration of study 1. Pregnant and lactating women up to 6 months post-partum will receive 30 eggs every 2 weeks and will be encouraged to eat 2 eggs per day. Once the child turns 6 months, the families will receive 15 eggs every 2 weeks and the mothers will be encouraged to feed the child 1 egg per day. The eggs will be purchased regularly from carefully selected and monitored suppliers. All suppliers are approved by the County Public Health Officer and have food handling certificates. Additionally, all warehouse staff have food handling certificates. The warehouse where the eggs are stored has been assessed by the Public Health Officer and recommendations taken into account and modifications made. Approval has been given to store eggs in the climate-controlled section of the warehouse. The eggs will be distributed to the women every other week. The eggs will be distributed every other week in order to make sure only fresh eggs are consumed which should not pose any risk to the participants. The participants will further be sensitized on the dangers of consuming raw eggs and advised to always boil/fry the egg before consumption and the need of hygiene when preparing dishes containing eggs. As the regular consumption of eggs is not common, the benefits of egg consumption will be explained to the mothers. Adherence to egg consumption will be monitored by interviewing the mothers monthly.

Poultry (to all intervention households in study 2)
All intervention households in study 2 will receive 8 birds of chicken when they receive their first bundle of products. Chickens that have died from disease or accident will be replaced the following year.

Nutritionally enhanced seeds (to all intervention households in study 2)
Seeds for red onion and indigenous greens (managu and sukuma), all traditionally bred, will be provided to enrolled households in study 2 in March 2018 and March 2019 to align with planting. Red Onions and Sukuma Wiki seeds will be supplied by East African Seed based in Nairobi and Managu seeds will be supplied by Kenya Seed Company based in Kitale, Kenya.

Life stage appropriate nutrition and WASH trainings (to participating women in intervention group in study 1 and caregivers in intervention group in study 2)
In study 1, CHVs will deliver monthly trainings to groups of mothers (according to their life cycle) and will additionally provide home counselling visits twice per month. In study 2, monthly training meetings (1 module per meeting) will be held by 1AF trainers. Training modules are currently being developed and may be adjusted for the study. The initial set of modules is presented in Table 9.

Table 9: Nutrition and WASH training modules that will be administered

Module No.	Life cycle	Topic of training module
1	Pregnant women	Nutrition for pregnant women – Diversity and frequency, caloric needs
2	Pregnant women	Nutrition ANC care (folic acid, iron, deworming)
3	Pregnant women	Impact of family planning on the nutritional status of a pregnant woman
4	Pregnant women	Water treatment, storage, food sanitation and hygiene
5	Newborns (0 to 6 months)	Immediate breastfeeding, colostrum and milk production
6	Newborns (0 to 6 months)	Breastfeeding efficacy skills - Common problems - Positions
7	Newborns (0 to 6 months)	Milk Supply - Biology - Extraction - Storage
8	Newborns (0 to 6 months)	Breastfeeding on demand Feeding through illness
9	Newborns (0 to 6 months)	Nutrition for the breastfeeding mother
10	Children under five	Timely introduction to complementary foods
11	Children under five	Routine health services and disease prevention - Growth Monitoring - Vitamin A - Deworming - Immunity and nutrition
12	Children under five	Food diversity in child feeding - 6 months - 7 to 9 months - 9 to 11 months - 12 to 23 months - 24 to 59 months (study 2 only)
13	Children under five	Food frequency in child feeding - 6 months - 7 to 9 months - 9 to 11 months - 12 to 23 months - 24 to 59 months (study 2 only)
14	Children under five	Responsive feeding Feeding through illness
15	Children under five	Sanitation and hygiene - Safe food handling - Handling of child faeces
16	Children under five	Malnutrition
17	Children under five	Water - Treatment, handling and storage
18	Children under five	Hand washing
19	Children under five	Micronutrient Powders

SMS reminders on antenatal care and life stage appropriate nutrition (to pregnant women in intervention group in study 1)
Messages will be sent using the mHealth (Mobile Health) technology Medic Mobile. Pregnant women will register their phones. CHVs will receive weekly messages on study activities and reminders to relay to pregnant women about routine antenatal care. Further, messages on key nutrition, hygiene and health topics will be sent regularly. These messages are currently being adapted from Mobile Alliance for Maternal Action (MAMA) content and field-tested and content will be finalised before study start.

Agriculture-focused package (to all households in intervention and control group in study 1 and study 2)
The same agriculture intervention as in the control group will also be provided to the intervention group, as all the selected clusters are part of the 1AF agricultural programme. Agricultural training (every 2 weeks on average) will be provided to all households for free. Additionally, households can enrol for the following products on credit: compost boosters**,** cook stoves**,** seeds (onions, maize, indigenous greens, beans)**,** maize storage bags**,** drying tarps**,** trees**,** solar lights**,** fertilizer**,** actellic dust (insecticide), re-usable sanitary pads.

8. DATA COLLECTION

8.1 Training and management of data quality

Before field work starts, data collectors, CHV, and supervisors will undergo training which includes the data collection tools, interview techniques, anthropometry and blood sampling. The training will include both, theory and practice, as well as a field test to optimize and adjust the questionnaires and procedures. Pre- and post-tests will determine the most suitable candidates and only those who pass the tests will be eligible for recruitment, starting with those with the best results. Therefore, the number of training participants will be 30% higher than actually needed; this will allow selection of the best performing from a large pool and also yield a list of potential substitute candidates should some field staff no longer be available.

Field staff interviewing participants will administer the questionnaires to each other and enter data into the tablets during the training. This will also help to revise the questionnaires based on any programming or survey wording errors. For anthropometry, a rigorous standardization practice will be conducted and the performance of each data collector (1AF enumerators) carefully evaluated so as to ensure highest quality of anthropometric measurements. The phlebotomists (lab technicians) will be specifically trained on capillary blood sampling by fingerprick and heelprick and on the use of the on-site diagnostic tests (HemoCue analyser and RDTs for malaria) as well as on the blood processing steps and storage of serum samples for later analysis of micronutrient status.

Prior to the start of the field work in the selected clusters, the teams will undergo a 2-day pilot test carried out in two clusters that are not part of the study. All steps of recruitment and data collection will be carried out as if it were for the study (including selection procedures, interviews, anthropometry, and blood sampling). Prior to each of the larger follow-up visits for study 1 (round 3, 4 and 5) and prior to each follow up round in study 2, a refresher training will be conducted on all team members.
During the main rounds of assessment, international experts will be present during the initial data collection period to closely supervise fieldwork in order to ensure that procedures are being followed closely.

To ensure a high quality of data collection, SOPs will be developed for the different persons involved in the study (SOPs for interviewers, phlebotomists, anthropometrists, team leaders and supervisors). Questionnaire-based data as well as anthropometric and blood-based data will be collected electronically in the field. That way real-time data monitoring will be conducted on an on-going basis in order to provide immediate feedback to the data collectors in case of sub-optimal data quality. In detail, all questionnaire-based data will be collected electronically using tablets and multiple forms for each study visit. They will be directly captured in a tablet. A paper form will be used for the collection of anthropometric and blood sampling results data as this will partly take place at a central place and will be recorded by other people than the questionnaire-based information. This also ensures source data to be available for the primary and main secondary indicators. Anthropometric and blood sampling data and results will be data entered into the tablet in the evening by the interviewer. All electronically captured data will be transferred to the appropriate password secured CommCare platform and will be available for data monitoring, cleaning and analysis for specific investigators.
The CommCare interface enables to enter validation conditions for each question/parameter, which will be set in order to minimise the entry of wrong data (e.g. limiting the entry for gestational age to 2-45). The data will also be checked in the CommCare database. Additionally, regular back-checks will be conducted. For these, 10-15% of participants will be randomly re-surveyed on a selected subset of

questions to assess errors. Any enumerator with high error rates will be held back for retraining. Enumerators found falsifying data through the back-check process will be fired.

Currently, a pilot study mimicking study 1 recruitment and distribution of interventions is being conducted and results will be taken into account in the final planning and training of field staff of study 1.

8.2 Quantitative data collection

For the **primary outcome**, change in LAZ between birth and 24 months of age in study 1 and over the course of the 2 years programme activity in study 2, **length** will be measured at one or two central places in each selected cluster that are well accepted by the public (e.g. health post, house of village head or midwife). The length measurement will always be conducted by two trained people independently (duplicate). If the length differs by more than 7 mm, which was set as the maximum allowable difference for acceptable precision (to achieve a rate of re-measurement of around 5%) between the measurement of two observers in a big standardization session [49], the electronic data-capturing device will prompt the anthropometrists to repeat both measurements. If a child is less than 24 month, the child's length will be measured lying down (recumbent) using a length board, which will be placed on a flat, stable surface such as a table. If the child is aged 24 month or older, standing height will be measured unless the child is unable to stand. A height board installed at a right angle between a level floor and against a straight, vertical surface such as a wall or pillar will be used.

For the **anthropometric secondary outcomes**, proportion of stunted children (LAZ<-2SD), length will be measured as described for the primary outcome above in both studies. Additionally, child weight will be measured using a calibrated infant scale placed on a horizontal, stable and flat surface that will be checked with a test weight every day before starting the measurements and head circumference (HC, only in study 1) will be measured using a MUAC/HC tape. All assessments will be done in duplicate by two different anthropometrists. A maximum allowable difference between the two data collectors of 100 g will be allowed for weight and 5.0 mm for HC [49]. In study 1, the measurement of MUAC will be used to identify the proportion of malnourished women (MUAC < 23 cm). MUAC will be measured on the left arm (hanging to the side of the body and relaxed) after having identified and marked the midpoint of the upper arm using a MUAC tape. All anthropometric measurements will be conducted by trained and standardized anthropometrists. Additionally, height and weight will be measured in women using the standard procedures as described above.

Blood-based secondary outcomes measured in children in study 1 include: Haemoglobin concentration measured at birth and 6 and 24 months of age will be used to assess the change in haemoglobin concentration and proportion with anaemia (Hb< 11g/dL). SF (serum ferritin), CRP (C-reactive protein) and AGP (alpha 1- acid glycoprotein) measured at 6 and 24 months of age will be used to assess the proportion with inflammation-adjusted iron deficiency (SF<12 µg/L) and the change in proportion with inflammation-adjusted iron deficiency. RBP (retinol binding protein), CRP and AGP measured at 6 and 24 months of age will be used to assess the proportion with inflammation-adjusted vitamin A deficiency (RBP<0.7 µmol/L) and the change of proportion with inflammation-adjusted vitamin A deficiency.

Blood-based secondary outcomes measured in pregnant women include: Haemoglobin concentration measured at 34 weeks gestation and 6 months postpartum will be used to assess the change in haemoglobin concentration, the proportion with anaemia (Hb < 11 g/dL), and the change in the proportion with anaemia. SF, CRP and AGP measured at 34 weeks gestation will be used to assess the proportion with inflammation-adjusted iron deficiency (SF<15 µg/L). RBP, CRP and AGP measured at 34 weeks gestation will be used to assess the proportion with inflammation-adjusted vitamin A deficiency (RBP<0.7 µmol/L).
The measurement of haemoglobin will be undertaken on-site using the HemoCue™ device and commercially available control blood. The control blood will be used every morning before measuring any participant's blood sample. SF, RBP, CRP and AGP will be measured using the enzyme linked immunosorbent assay (ELISA) technique at the VitMin laboratory in Germany which is using control samples to assure high quality results. At the different time points, capillary blood will be collected from mothers and eligible children by experienced technicians trained for the techniques used in this evaluation. For children below 12 months of age, capillary blood will be collected by sticking the heel

using lancets appropriate for this age group. For women and children above 12 months old, capillary blood will be collected by sticking the middle or ring finger. The first blood drop will be swiped, the second and third drop collected (approximately 10 µl) will be used for the on-site analysis of anaemia and malaria (see section 9.2.3 for malaria as an outcome). This will be done in rounds 1, 2, and 4 in women, and in rounds 3, 4, and 5 for children. Additionally, micronutrient status will be assessed at round 2 in women and rounds 4 and 5 in children for which approximately 300µl of capillary blood will be collected in Microtainers™ (Sarstedt, Germany) and stored in portable cold boxes for the day and later aliquoting and freezing of the serum.

Diarrhoea incidence rate between birth and 24 months of age will be assessed monthly between study rounds 3 and 5 using questionnaires by trained enumerators.

8.2.1 Data collection instruments

In all assessment rounds in study 1 and 2, questionnaires will be administered to the participant or the participants' mother/caregiver by previously trained study staff. The type of modules and in which study they are used are summarized in Table 10.

Table 10: Summary of modules used to collect information through questionnaires.

Module	Study 1	Study 2
Household demographics	x	x
Household characteristics	x	x
Maternal education/occupation	x	x
Maternal information on pregnancies and child birth	x	x
Knowledge, attitude and practices (KAP) of dietary and nutrition practices during pregnancy and lactation	x	
Woman dietary diversity	x	
Antenatal care	x	
Postnatal care	x	
Knowledge and consumption of study specific intervention products	x	x
Knowledge and practices on Water, sanitation and hygiene (WASH)	x	x
Initiation of breastfeeding	x	x
Infant and young child feeding indicators (IYCF)	x	x
Child illness	x	x
Adherence	x	x

8.3 Qualitative data collection

Not applicable

8.4 Ethical issues

The decision of the Ethics Committee of the Canton of Zurich (KEK Zurich) regarding a 'no objection statement' as well as the decision of the AMREF's (African Medical & Research Foundation) Ethics & Scientific Review Committee (ESRC) in Kenya concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study will only begin once approval (or no objection statement) from both Ethics Committees has been received. Any additional requirements imposed by the ESRC will be implemented to the best possible. Substantial amendments are only implemented following prior approval of the ESRC.

Previously trained 1AF enumerators will explain to each participant in study 1 or to caregivers of children participating in study 2 the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. The information will be provided in the language best understood by the participant/caregiver (Swahili and Luhya). Each participant or caregiver will be informed that the participation in the study is voluntary and that she may withdraw herself or her child from the study at any time and that withdrawal of consent will not affect her and/or her child's subsequent medical assistance and treatment.

The participant will be informed that her and or/her child's medical records may be examined by authorised individuals other than health care staff if need arises.

All participants for the study or caregivers of participating children will be provided a participant information sheet (in Swahili or Luhya) and a consent form describing the study and providing sufficient information for the participant or the caregiver to make an informed decision about their own or their child's participation in the study. In case of illiterate participants/caregivers, the study will be explained in the presence of an impartial witness or read out by the impartial witness that is chosen by the potential study participant. Enough time will be given to the participants/caregivers to decide whether to participate or not. This is particularly important as in some circumstances the caregiver/pregnant woman may need to await her husband's/the head of household's approval for participation.

The participant information sheet and the consent form will be submitted to the KEK Zurich and to the local ESRC to be reviewed and approved. The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure.
The participant/caregiver of participating children will read, or have read in case of illiterate participants in the presence of an impartial witness, and consider the statement before signing and dating the informed consent form, and will be given a copy of the signed document. The consent will also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

For study 1, consent will be taken from the pregnant woman for herself and her offspring. Participants will not receive any compensation for their participation but will receive baby clothing and blankets as a small incentive (both control and intervention group).
For study 2, consent will be taken from the caregiver of the participating child. Participants will not receive any compensation for their participation but will receive blankets as a small incentive (both control and intervention group).

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants will be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.
Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited, except in circumstances where medical follow-up is required pursuant to information obtained. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.
Direct access to source documents will only be permitted to the advisory board (see below) members if requested by them. Access to all study related documents (protocol, questionnaires, dataset, randomization code, etc.) during and after the study will be managed by the sponsor-investigator who will delegate access to the respective documents.

Data from the two studies will be stored on CommCare's secure cloud server. Only selected 1AF Kenya Monitoring & Evaluation staff and GroundWork investigators will have access to the password-protected data on CommCare. They will be able to access the data as it is uploaded from the tablets. De-identified data will be downloaded regularly on password-protected servers for monitoring purposes, which will serve as a back-up.

The serum samples collected for the analysis of micronutrient status will be stored until final lab results are received and validated from the VitMin Lab. Six months after the results are considered as final, the samples will be destroyed. The duplicate sample, which will be held as back-up samples in Kenya in case something happens to the samples during shipment to Germany, will also be destroyed six months after results are considered final.

The investigators suggest having an advisory board that will review the protocol, tools and baseline reports, followed by moderated teleconferences to discuss course correction. They would also review the final reports. The following people have accepted to be on the advisory board:

Prof. James Jay Berkley, KEMRI-Wellcome Trust, Kilifi, Kenya
Dr. Sophie Moore, King's College London, London, UK
Dr. Seth Adu-Afarwuah, University of Ghana, Accra, Ghana

9. DATA PROCESSING AND ANALYSIS

9.1 Data processing

The CommCare platform will be used for this study. All forms will be programmed by Kelvin Musau (Monitoring & Evaluation Nutrition Associate and local PI) and the CommCare coding will be verified by an experienced Monitoring & Evaluation Project Specialist. Most data will be collected electronically using tablets and once collected will automatically be transferred and stored on 1AF's account on the CommCare server. All forms will be pretested in the field. Data captured on paper forms first (anthropometry and blood results) will be entered into the tablets in the evening of the same day and together with that days participant's form uploaded to CommCare. Incoming data will be checked regularly, on a daily base initially, and edited according to query forms.

9.2 Data analysis

The intervention group will be compared to the control group in both studies using the intention to treat approach as this is not a strictly controlled clinical trial and adherence is one of the outcomes.

Data analysis will be done researcher-blinded, meaning that the data analyst will not be provided with the keys to the group assignments before completion of data analysis. A data analysis plan will be elaborated once the study protocol is approved by the ethics committee and well in advance of the actual data analysis.

9.2.1 Primary analysis

The intended primary analysis (primary outcome) will be conducted by Bradley Woodruff using SPSS once a clean dataset is available.

Study 1 and 2:
Anthropometric indices derived from measurements collected during study 1 and study 2 will be calculated using the WHO Child Growth Standard. Differences will be considered significant if $p < 0.05$, and interactions will be considered significant if $p < 0.1$. Covariates will include at least household socio-economic status, sex, and age. Regression models will be applied to analyse the effect of programme adherence.
Mean change in LAZ or HAZ measures will be compared between the two study arms in both studies using linear regression analysis. Details of the statistical methods will be outlined in the statistical analysis plan that will be elaborated once the protocol has been reviewed by the advisory board and approved by the ethics committees.

9.2.2 Secondary analyses

The intended secondary analysis (secondary outcomes) will be conducted by Bradley Woodruff using SPSS once a clean dataset is available.

Study 1 and 2 (main secondary analyses):
For both studies, the values for continuous variables, including MUAC, birth weight, birth length, HC, Hb, SF, RBP, CRP, AGP, TfR (transferrin receptor), and anthropometric indices, will be checked for normality of distribution, and non-normally distributed variables will be either transformed to obtain normality or analysed using non-parametric methods. Mean change in outcome measures will be compared between the two study arms using simple paired t-tests or for multivariate analysis using linear regression analysis. All measures of precision and statistical significance will be adjusted for the complex sampling employed. Differences will be considered significant if $p < 0.05$, and interactions will be considered significant if $p < 0.1$. Covariates will include at least household socio-economic status, sex, and age. Regression models will be applied to analyse the effect of programme adherence.
Details of the statistical methods will be outlined in the statistical analysis plan that will be elaborated once the protocol has been reviewed by the advisory board and approved by the ethics committees.

Study 1 and 2 (additional secondary analyses):

We will look at potential negative effects of the intervention and will assess whether there is a difference between the intervention and control group with respect to:

- a lower proportion of the children less than 6 months of age are exclusively breastfed
- complementary food is introduced too early
- dietary diversity is lower in pregnant/lactating women and children
- there is an increase of overweight and obesity in pregnant/lactating women and children
- there is an increase of morbidity incidences such as diarrhoea in the children (this is monitored monthly)

Overweight and obesity will be defined as BMI > 25 and 30 for the women, respectively. For children, overweight will be defined as a weight-for-height z-score of greater than +2.0 but less than or equal to +3.0 and obesity as a weight-for-height z-score greater than +3.0.
Details of the statistical methods will be outlined in the statistical analysis plan that will be elaborated once the protocol has been reviewed by the advisory board and approved by the ethics committees.

9.2.3 Interim analyses

An interim analysis comparing birth length and weight between the intervention and control group as well as indicators collected during pregnancy (MUAC, weight, haemoglobin) will be conducted.
Further, small basic interim analysis after each round of data collection will be conducted in order to use them for interim reports which will only contain the most highly-relevant information and will be sent to the advisory board members.
These interim analyses will be performed by another statistician in order to make sure that Bradley Woodruff remains blinded for the main analysis.

9.2.4 Handling of missing data and drop-outs

In both studies, subjects without one of a paired measurement will not be included in the final analysis of change over time. In addition, in both studies, subjects missing the single outcome measurement will be included in the analysis of change over time. As a result, we will assume that drop-outs of subjects missing a specific measurement will not differ substantially from those subjects for whom complete measurements are available.

10. PLAN FOR COMMUNICATING FINDINGS OF THE STUDY

10.1 Dissemination strategy

The dissemination of the evaluation will be conducted using four concurrent dissemination activities.

1. Reporting of study results: The results from the various studies will be documented in multiple study reports, produced following each round of data collection for the two studies. Reports containing data from one data collection round will contain only the most highly-relevant information to make programmatic decisions. Following the completion of all data collection rounds for each evaluation activity, a comprehensive report will be produced containing all relevant information.
2. Peer-reviewed publications: Following completion of the various reports, further analyses on the data will be conducted and manuscript(s) will be submitted to peer-reviewed journals.
3. Presentation at national and international meetings and conferences: Following the completion of the study reports, results, in part or as a whole, will be presented to stakeholders. In addition, abstracts describing key results will be submitted for presentation at relevant meetings and conferences.
4. At the end of the study, the participating communities will be informed about the results of the study. This will include findings on the main study outcomes but also findings on product adherence and acceptability of the participating women and children. Possible next steps depending on the findings will also be highlighted to the communities.

10.2 Involvement of stakeholders

After receiving all the necessary ethics and government approvals, One Acre Fund will conduct introductory meetings with County health management teams, government administration and any present partner working on nutrition in order to introduce the two studies to these stakeholders. Further, the aim and reason of the two studies will be introduced to all community members through sensitization meetings. A focus will be on the interventions being tested and the community's equal chance of being selected into the intervention or control group. We also plan to provide process evaluation and reporting of indicators to relevant stakeholders as part of routine program updates and to strengthen working relations.

10.3 Potential policy implications

The two studies compare a purely agricultural intervention with an integrated intervention including nutrition and hygiene interventions in addition to the agricultural approach. If the study results show improved growth and micronutrient status in children in the integrated approach group when compared to the agricultural group alone, this may result in changing some of the existing policies towards a more integrated approach rather than trying to improve agriculture alone, nutrition alone or hygiene (WASH) alone. Further, in case of positive results with respect to growth and anemia prevention in study 1, this may help to formulate guidelines for the use of LNS in a non-emergency context adding to the growing body of evidence that LNS may indeed help in improving growth and development in low-income countries. Similarly, study 2 may add to the existing evidence of the effect of micronutrient powders on micronutrient status. The results may also lead to a change of local nutrition guidelines.

By referring study participants who are malnourished, anaemic or have a positive RDT result for malaria accompanied by fever (>37.5°C), using the existing referral system this may indicate where specific treatment centres for malnutrition and anaemia are most required and could help in improving the situation.

In summary, children and pregnant women in other regions of Kenya and other parts of the world with similar climatic and environmental settings may benefit from the study results, which will hopefully help in formulating guidelines and policies.

11. STUDY LIMITATIONS AND RISKS

11.1 Limitations of study design

The longitudinal design in both studies is a strong design as within subject comparison is possible, particularly for anthropometry and blood-based data. This design however has its drawbacks, particularly when using questionnaires, as participants may remember questions and may be aware what the answers should be and thereby introducing bias. This is particularly a limitation for study 1 in which some questionnaires are administered in consecutive rounds that may only be apart from each other by a couple of months. This is less of an issue in study two in which the assessment rounds are 2 years apart.

For study 2, choosing a longitudinal design forces us to widen the age range at admission in order to keep the study size manageable. This may lead to a more heterogeneous study population and bears the potential to mask certain findings that are more probable to take place in a very narrow age range only.

By conducting the studies in a rather narrow area of Western Kenya, the findings might not be directly extrapolated to the rest of the country or to other countries. However, results might be applicable to many countries in Africa where farming is the main source of income/occupation.

11.2 Major assumptions

In both studies, subjects without one of a paired measurement will not be included in the final analysis of change over time. In addition, in both studies, subjects missing the single outcome measurement

will be included in the analysis of change over time. As a result, we will assume that drop-outs of subjects missing a specific measurement will not differ substantially from those subjects for whom complete measurements are available.

12. MANAGEMENT AND ORGANIZATION OF THE STUDY

12.1 Team members and roles

The studies will be mainly managed and led by the Sponsor-Investigator, Dr. Fabian Rohner, the Principal Investigator, Dr. Rita Wegmüller and the Local Principal Investigator Mr. Kelvin Musau. They will be supported in different areas by all the other investigators. Detailed responsibilities of each team member are illustrated in Table 11.

Table 11: Responsibilities of team members

Name	Role in study	Responsibilities
Dr. Fabian Rohner	Sponsor-Investigator	- Overall management of the studies - Supervision of training of investigators - Monitoring of studies - Ensuring all the ethics approvals are obtained - Ensuring that the trial is conducted according to the protocol - Ensure that required infrastructure, equipment, expertise, and trained staff is available - Ensure SAEs are reported to the ethics committee
Dr. Rita Wegmüller	Principal Investigator	- Ensure studies are conducted according to the protocol - Development of SOPs - Development, testing and revision of study forms - Conduct of study staff training - Regular data monitoring and data quality checks - Ensure AEs and SAEs are collected and reported - Coordinate lab analysis - Write up of final study report
Mr. Kelvin Musau	Local Principal Investigator	- Assist in the development, testing and revision of study forms - Programming of study forms - Ensure studies are conducted according to the protocol - Manage the field teams (interviewers, nurses) - Conduct of study staff training - Daily data monitoring - Daily monitoring of field staff - Conduct and evaluate regular quality checks in the field - Ensure AEs and SAEs are collected and reported - Ensure participant information is explained accurately - Maintain accurate records including consent forms
Ms. Haley Kawaja	Co-Principal Investigator	- Content creation for nutrition trainings and lessons - Lead the trial design from a process and logistical perspective - Support development and review of study protocols and implementation guides - Lead product vetting and product ordering through

		local and global procurement means - Oversee the logistical coordination of storing products, packaging products in the warehouses, and delivering products to participants - Support in recruitment, interviewing and hiring of staff - Oversee printing and procurement of all study materials
Ms Marion Kiprotich	Co-Principal Investigator	- Government relations and policy - Interpret and explain laws and policies applicable to this study. - Ensures study compliance with govt and regulators-NACOSTI/AMREF/KNDI/PPB. - Training of nutrition staff on Anthropometry, standardization and quality checks. - Timely reporting of SAEs/AEs to IRB - Work closely with study doctor on referrals and follow ups - Periodic reports to government/stakeholders and regulators - Point person between One Acre Fund & AMREF ESRC
Dr. med. Tim Chindia	Co-Investigator (Study Clinician)	- Provide for study-related medical care of study participants - Facilitate referrals - Ensure correct and complete adverse event and serious adverse event assessment and reporting
Ms. Emily Lloyd	Co-Investigator	- Assist PIs in study implementation - Assist PIs in training of staff - Product procurement: ensure that sufficient supply of intervention products are available - Donor communications
Dr. Maya Duru	Co-Investigator	- Advise on research design - Ensure data quality - Advise on final data analysis - Contribute to the final reporting
Dr. med. Bradley A. Woodruff	Co-Investigator (Statistician)	- Develop statistical analysis plan - Conduct statistical analysis - Conduct second evaluation of SAEs
Dr. Nicolai Petry	Co-Investigator	- Assist PI in the development of forms - Assist PI in staff training - Contribute to the final reporting
Mr. James Wirth	Co-Investigator	- Assist PI in staff training - Contribute to the final reporting

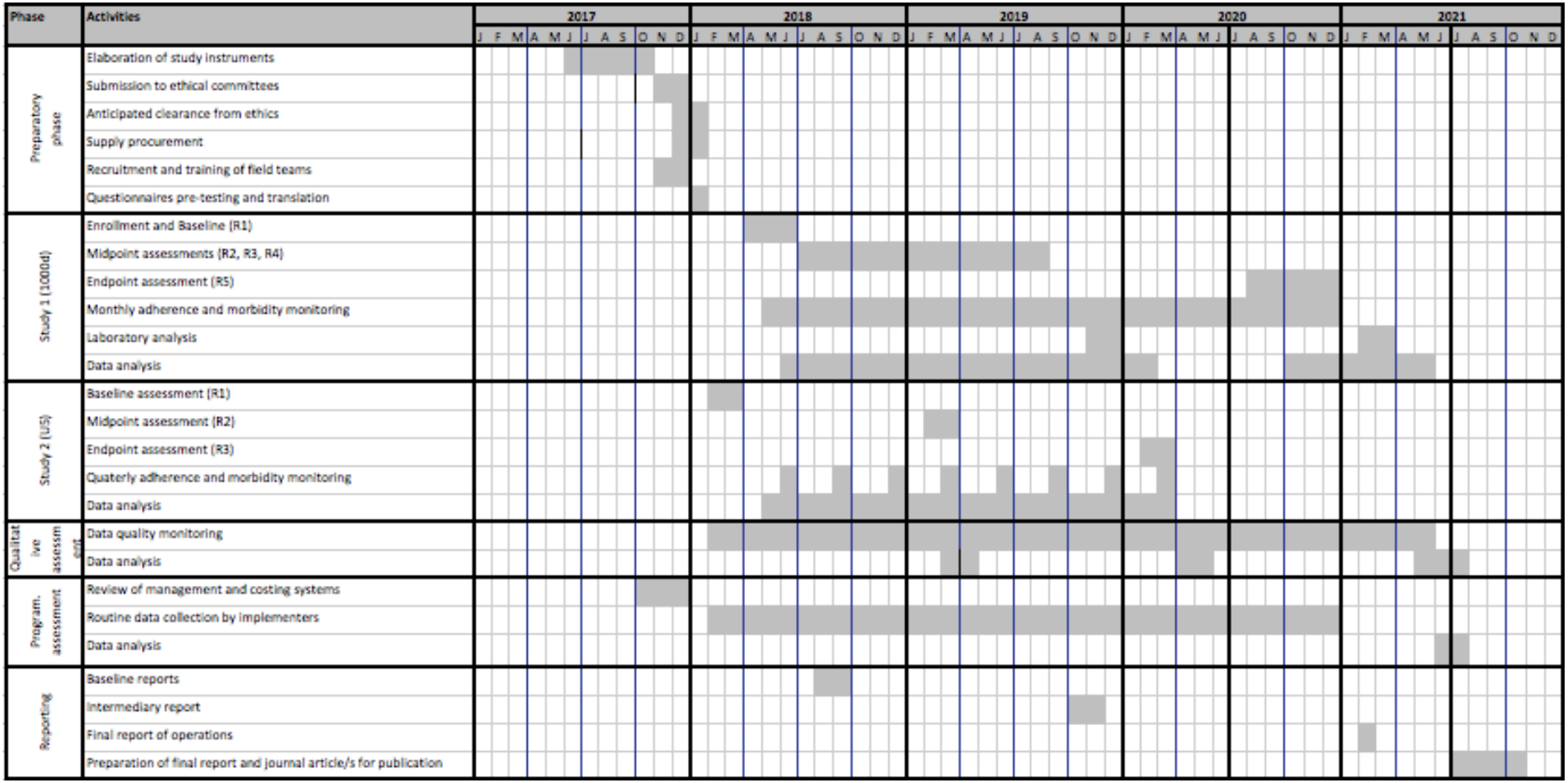
12.2 Other resources and facilities

Not applicable

12.3 Timelines

The detailed schedule of the two studies is outlined below (Table 12). The training of study 2 staff is planned to start in late January while the training for study 1 is planned for April.

Table 12: Gant chart



12.4 Budget

The overall budget that is available to conduct the two studies is $ 2,055,458. An overview of the detailed budget categories by year is given in Table 13.

Table 13: Budget summary by budget category and year

Summary by budget category	**Cost**		
	Year 1	**Year 2**	**Year 3**
Staff - research international	$74'820	$72'180	$134'880
Staff - research national	$93'100	$93'100	$93'100
Staff - program international	$59'850	$59'850	$59'850
Staff - program national	$119'700	$119'700	$119'700
International travel	$18'069	$16'999	$11'034
National travels	$59'302	$54'452	$6'552
Program supplies (product bundles)	$174'420	$171'420	$109'420
Medical evaluations (referrals, clinician)	$23'500	$23'500	$23'500
Data collection - equipment, commodities	$37'716	$26'016	$56'616
Laboratory analysis and shipment	$14'620	$14'620	$48'620
Program and govt staff training	$66'600	$21'600	$16'600
Other costs (translation, enumerator training...)	$13'936	$6'436	$5'236
Subtotal	$615'580	$492'820	$498'055
Indirect cost	$7'874	$6'605	$14'368
Total	**$763'506**	**$639'477**	**$652'475**

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14. APPENDICES

14.1 Participant information and consent forms

Study 1 English (version 2)

Study 1 Swahili (version 2)

Study 1 Luhya (version 2)

Study 2 English (version 2)

Study 2 Swahili (version 2)

Study 2 Luhya (version 2)

14.2 Questionnaires/assessment forms

Enrolment form study 1

Round 1 form study 1 (version 2)

Round 2 form study 1 (version 2)

Round 3 form study 1 (version 2)

Round 4 form study 1 (version 2)

Round 5 form study 1 (version 2)

Monthly adherence and morbidity questionnaires study 1

Referral form study 1

Enrolment form study 2

Round 1 form study 2

Round 2 form study 2

Round 3 form study 2

Quarterly adherence and morbidity monitoring questionnaire study 2

Referral form study 2

Adverse event reporting form study 1 & 2

Serious adverse event reporting form study 1 & 2

14.3 Curriculum vitae of investigators and certificates (documents of 2 local Co-PIs added)

14.4 IRB approval letter from PI's country

14.5 Signed government approval letter

14.6 Pharmacy and Poisons Board retention certificate & Import Permit for LNS

14.7 SOP on Blood collection and processing