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Effect of balanced energy-protein supplementation during pregnancy and lactation on birth outcomes and infant growth in rural Burkina Faso: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Adequate nutrition during pregnancy is crucial to both mother and child. Maternal malnutrition can be the cause of stillbirth or lead to poor birth outcomes such as preterm delivery and small-for-gestational-age newborns. There is a probable positive effect of providing pregnant women a balanced energy-protein (BEP) food supplement, but more evidence is needed. The MIcronutriments pour la SAnté de la Mère et de l'Enfant (MISAME) III project aims to improve birth outcomes and infant growth by testing a BEP supplement during pregnancy and lactation in rural Burkina Faso. This paper describes the study protocol.

Methods and analysis MISAME-III is a four-arm individually randomised efficacy trial implemented in six rural health centre catchments areas in the district of Houndé. Eligible pregnant women, aged between 15 and 40 years old and living in the study areas, will be enrolled. Women will be randomly assigned to one of the four study groups: (1) prenatal intervention only, (2) postnatal intervention only, (3) prenatal and postnatal intervention or (4) no prenatal or postnatal intervention. The intervention group will receive the BEP supplement and iron/folic acid (IFA) tablets, while the control group will only receive the IFA tablets following the national health protocol. Consumption will be supervised by trained village women on a daily basis by means of home visits. The primary outcomes are small-for-gestational age at birth and length-for-age z-score at 6 months of age. Secondary outcomes will be measured at birth and during the first 6 months of the infants' life. Women will be enrolled from October 2019 until the total sample size is reached.

Ethics and dissemination MISAME-III has been reviewed and approved by the University Hospital of Ghent and the ethics committee of Centre Muraz, Burkina Faso. Informed consent will be obtained. Results will be published in relevant journals and shared with other researchers and public health institutions.

Trial registration number NCT03533712.

Strengths and limitations of this study

- This trial will help to fill the evidence gap on the effect of balanced energy-protein (BEP) supplements in pregnant and lactating women on birth outcomes and infant growth.
- Formative research to select the most suitable BEP supplement ensured that the selected BEP is well accepted by the study population.
- The daily intake of BEP supplements and iron/folic acid tablets during pregnancy and lactation will be directly observed by study workers.
- This study will assess the impact of factorial combinations of prenatal and postnatal BEP on child growth to elucidate the relative importance of BEP during pregnancy and/or early lactation.
- Blinding of study participants and staff members will not be possible, as the supplements are identifiable.

INTRODUCTION

Pregnancy is a challenging period in the life of many women in low-income and middle-income countries (LMICs). Maternal mortality remains high, and many neonates suffer from premature delivery and/or intrauterine growth retardation, both in length and in weight accumulation.[1] An indicator to measure neonatal growth is small-for-gestational age (SGA). SGA is defined as a birth weight below the 10th percentile of a standard optimal reference population for a given gestational age and sex.[2] SGA is often caused by growth restriction in the womb and has been associated with neonatal and postneonatal mortality.[2] It has also been linked to an increased risk of morbidity later

in life, especially non-communicable diseases.[3] SGA affected 23.3 million term children in LMICs in 2012.[4] Adequate nutrition during pregnancy is crucial for optimal maternal and newborn health,[5 6] and maternal malnutrition has been associated with fetal growth restriction.[7] An adequate dietary balance is necessary to ensure sufficient energy intake for adequate growth of the fetus.[8] Unfortunately, maternal undernutrition remains a public health challenge in regions across sub-Saharan Africa and Asia.[9 10]

Several types of food supplements have been developed and evaluated over the past years. A positive effect of multiple micronutrient supplements (MMS) during pregnancy on birth outcomes has been found in previous studies.[11] Keats *et al*[11] concluded in their review that MMS during pregnancy gave a probable reduction in SGA and preterm births and can thus be used for future guidance. According to a multicountry randomised controlled trial (RCT) done in LMICs, a positive effect of lipid-based nutrient supplements on fetal growth-related birth outcomes can be seen when starting supplementation before conception or during the first trimester.[12] Moreover, the latest evidence indicates a possible positive effect of providing pregnant women a balanced energyprotein (BEP) food supplement.[5 13–15] In line with that evidence, the 2016 WHO's antenatal care guidelines state that pregnant women in undernourished populations should receive, depending on the context, BEP supplements to reduce the risk of stillbirth and SGA.[6] Researchers, however, still highlight the limited amount of evidence and a need to evaluate the effect of balanced supplements on birth outcomes, such as SGA.[5 13] Experimental trials of high-quality and large sample sizes, especially in undernourished pregnant women, are thus needed.[13] Following this recommendation, compositional guidance for a ready-to-use food supplement for pregnant women was developed by the Bill and Melinda Gates Foundation (BMGF) in 2016.[16]

Two previous projects, MIcronutriments pour la SAnté de la Mère et de l'Enfant (MISAME) I and II, conducted in Burkina Faso, investigated the effect of supplementation during pregnancy and the effect on birth outcomes in infants.[17 18] MISAME-I compared the effect of the UNICEF/WHO/UNU international multiple micronutrient preparation (UNIMMAP) with the effect of iron/folic acid (IFA) alone on fetal growth in a double-blind RCT and concluded that UNIMMAP modestly but significantly increased fetal growth.[17] The second study (MISAME-II) assessed the effect of a lipid-based nutrient supplement fortified with UNIMMAP compared with a UNIMMAP tablet during pregnancy in an open-label, individually randomised controlled trial on birth anthropometry. It was found that combining energy with micronutrients during the prenatal phase led to larger birth lengths.[18] Since MISAME-II used the UNIMMAP as a control, a complete assessment of the impact of the fortified lipid-based UNIMMAP was not possible. Therefore, MISAME-III will study the effect of a BEP supplementation, compared with a control group, and extend the supplementation postnatally to investigate the net contribution of prenatal and postnatal BEP supplementation on child linear growth up to 6 months of age.

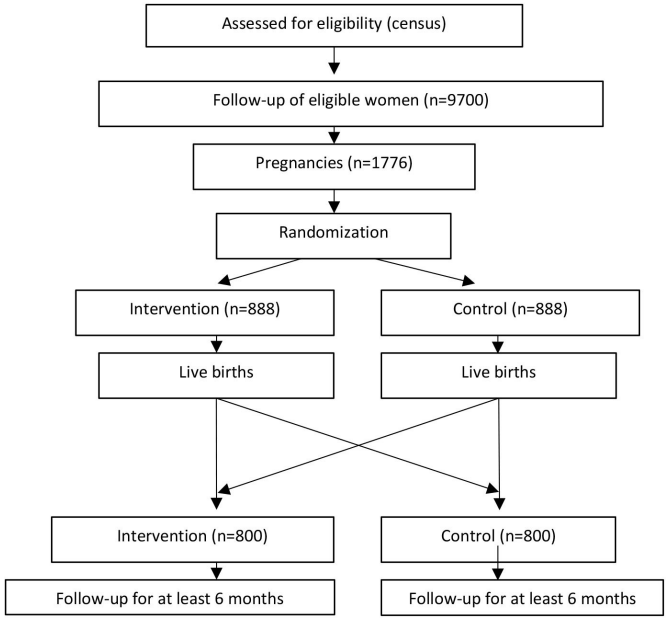

Figure 1 Study design of the randomised controlled trial.

In summary, the MISAME-III study hypothesises that: (1) providing women with a BEP supplement during pregnancy will decrease the incidence of SGA compared with the control group; and (2) providing them with a BEP supplement during the postnatal period will increase children's length by the age of 6 months compared with the control group.

METHODS

This protocol has been developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines (online supplemental file 1).

MISAME-III study design

The MISAME-III project is an individually randomised 2×2 factorial efficacy trial aiming to improve birth outcomes and infant growth in rural Burkina Faso by testing a BEP supplement during pregnancy and lactation (figure 1). At inclusion, pregnant women will be individually and randomly allocated to a prenatal intervention or control group and a postnatal intervention or control group. The intervention group will receive a daily BEP supplement to be consumed under supervision for the duration of pregnancy/lactation. Both intervention and control groups will receive the standard IFA tablet through the national antenatal care. In addition to the main trial, we propose a number of substudies to test specific hypotheses in a subsample of pregnant/lactating women and children. MISAME-III began with a formative study to identify the preferred product type for the provision of a fortified BEP supplement during the RCT.

Study setting

The study will be conducted in the district of Houndé in Burkina Faso, a landlocked country situated in West-Africa; similar to the previous MISAME studies, Burkina Faso has an infant mortality rate of 53 per 1.000 live births,[19] with an estimated Low Birth Weight (LBW) prevalence at 14% in 2013.[20] The prevalence of SGA has been estimated to be between 32.2% and 41.6% in the district of Houndé.[17] The Demographic and Health Survey of 2010 reported that 16% of women had a body mass index (BMI) below 18.5 kg/m^2, which indicates the presence of chronic energy deficiencies in the zone.[21] The highest prevalence can be found in the Eastern region, where 31% of women have a BMI lower than 18.5 kg/m^2, that is, low BMI.[22] Moreover, in particular, adolescent Burkinabèe girls between the age of 15 and 19 years have a low BMI, with an estimated prevalence of 23%.[23] Micronutrient deficiencies also remain a major problem in both infants and women of reproductive age in the country.[23 24]

The climate of the country is Sudano-Sahelian, with a dry season from October to March/April and a rainy season from May until September/October. The diet is essentially cereal based[25] with maize as the main staple food.[26]

MISAME-III will be conducted in the same health district where the two previous MISAME studies were organised. The study villages are concentrated around six health centres, which are within an accessible range from the district hospital. A list of all study sites can be found on: www.misame3.ugent.be

Study population and recruitment

Women living in the study villages and aged between 15 and 40 years will be identified through a census. The villages were selected based on their accessibility and distance to the nearest health centre, number of facility-based deliveries per year and their agricultural model as some households tend to reside on their fields during the harvest season. Trained village women (femme accompagnante (FA)), selected in collaboration with the community leaders, will visit the households every 5 weeks to ask about women's menstruation. In case of amenorrhoea, women will be sent to the nearest health centre for a pregnancy test and a first antenatal consultation by our project midwife when tested positive. An ultrasound examination will be completed soon after inclusion by the project medical doctor to assess gestational age. A baseline interview will also be done by the project interviewers to assess the household members' characteristics, household properties, water sanitation and hygiene (WASH) and household food security.

Inclusion criteria:

- Women between 15 and 40 years old at study inclusion.
- Confirmed pregnancy by a pregnancy test and ultrasound.
- Women who signed the informed consent form.

Exclusion criteria:

- Pregnancies >20 weeks of gestational age.
- Women planning on leaving the area during their pregnancy.
- Women planning on delivering outside the study area.
- Women who are allergic to peanuts.
- Women with multifetal gestations (exclusion from analysis).

FAs will be informed by the project midwife when a participant has been included. FAs will visit pregnant women on a daily basis to distribute the BEP supplement and/or IFA tablet and to supervise consumption. During the postnatal period, FAs will distribute the supplements and IFA tablets to the intervention group on a daily basis until 6 weeks after birth. From that moment onwards, they will receive a week's worth of BEP supplements. The postnatal control group will receive the IFA tablets on a daily basis during the first 6 weeks after birth, and participants will thereafter be visited once a week (without any supplementation) to minimise the effect of home visits. The FA will inform women on the supplement's function, the importance of antenatal visits during pregnancy, maintaining a healthy diversified diet, the importance of delivering at a health facility, the importance of exclusive breast feeding and the introduction of complementary foods at the age of 6 months. Throughout the study, the FAs will be supervised by project interviewers. Supervision visits will be conducted using Lot Quality Assurance Sampling schemes and empty sachet counts to ensure that study participant are visited according to the project protocol.

Manufacturing of 12 fortified BEP supplements and the formative study

Twelve fortified BEP supplements were pretested before the start of the RCT during a formative research phase. Several food manufacturing companies were invited to produce ready-to-use BEP supplements following the compositional guidelines proposed during an expert meeting hosted by the BMGF[16] in September 2016 (table 1). The BEP supplements had to be: (1) ready to consume, (2) not need a cold chain and (3) microbiologically stable.

Seven out of 12 supplements were characterised as sweet and five as savoury. Products were produced in different forms, including a biscuit, pillow, wafer, bar, paste, instant drink and soup.

In a first screening step of the formative study, the two most preferred BEP supplements were identified by using a combined evaluation approach consisting of a single meal test, sensory evaluation and focus group discussions, in a convenience sample of 40 pregnant women. In a next step, we compared the acceptability of the two preselected BEP supplements using a 10-week home-feeding study, with 80 pregnant women, to select to most preferred product for the RCT. We refer to both papers for detailed information.[27 28]

Study intervention

At inclusion, pregnant women will be randomly allocated to four different study groups: (1) prenatal intervention

Table 1 The compositional guidelines for macronutrients and micronutrients

Nutrition component	Target per serving
Total energy	250–500 kcal per serving.
Fat content	10%–60% of energy intake.
Protein content	16 g (14–18 g) with a digestible indispensable amino acid score of ≥0.9.
Carbohydrates	Between 45 g and 32 g per 100 g (added sucrose between 20 g and 10 g per 100 g).
Trans fats	<1% of energy intake.
Fatty acid	(Optional): min of 1.3 g of n-3 or 300 mg docosahexaenoic acid (DHA)+eicosapentaenoic acid (of which 200 mg DHA) to achieve a healthy n-6: ratio of the supplement of 5:1.
Micronutrients	Vitamin A, D, E, K, B1 (thiamin), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B9 (folate), B12 and C; minerals: iron, zinc, iodine, calcium, phosphorous, copper and selenium.
Optionally	Pantothenic acid, manganese, potassium, biotin and choline will be included.
	The final composition of the product will be determined by the selected product as the manufacturing process will influence the macronutrient composition.

only, (2) postnatal intervention only, (3) prenatal and postnatal intervention or (4) no prenatal and no postnatal intervention. Prenatal and postnatal supplementation will start right after inclusion and birth, respectively. The prenatal intervention group will receive the BEP supplement and IFA, while the control group will receive IFA tablets alone. The IFA tablets contain 65 mg iron and 0.4 mg folic acid. The postnatal intervention group will receive the BEP supplement for 6 months in combination with the IFA tablets for 6 weeks following the national protocol of Burkina Faso; the control group will receive IFA alone for 6 weeks.

Allocation/randomisation

We will apply a stratified permuted block randomisation schedule to allocate women to the prenatal intervention or control group and in a next step to allocate women to a postnatal intervention and control group. Per health centre (ie, stratum), women will be individually randomly in permuted blocks of 8 so that, per block, equal numbers are obtained in the prenatal intervention (n=4) and control (n=4) group and equal numbers are also obtained in the postnatal intervention (n=4) and control (n=4) group. The double random sequence will be generated before the start of the study using Stata V.15.1 (Statacorp, Texas, USA) by an external research analyst. The allocation group will be coded with two letters (A or B for the prenatal and Y or Z for the postnatal study group) and placed in a sequentially numbered sealed opaque envelopes by project employees, not in direct contact with participants. At study enrolment, the project midwife will draw the next sealed envelope and allocate the participant to the study group defined by the letter code in the envelope. Blinding of participants and community-based project workers will not be possible since the supplements are identifiable. Field staff responsible for measuring primary and secondary study outcomes are not directly involved in the daily supplementation of the study participants and can therefore be considered to be partially blinded.

Outcomes

Primary outcomes of the RCT

The trial has two primary study outcomes that will be used to assess the impact of the prenatal and the postnatal intervention, respectively:

- Incidence of SGA, defined as birth weight <10th centile of the Intergrowth 21st reference.[29]
- Length-for-age z-score (LAZ) calculated using the WHO 2006 growth reference at 6 months of age.[30]

Secondary outcomes of the RCT

A list of the trial's secondary outcomes can be found in table 2.

Birth weight measurements will be defined using the Intergrowth 21st reference,[29] and child anthropometry will be defined using the Child Growth Standards developed by the WHO.[30]

Outcomes of the substudies

Substudy 1: impact of the intervention on neonatal and maternal body composition 2–3 weeks after delivery.

Body composition will be determined in mother–child dyads by deuterium dilution and analysis of saliva by a Fourier Transform Infrared reader (Agilent FTIR 4500 series). The substudy will also assess if early gestation maternal BMI (defined as body weight in kilograms divided by the square of height in metres) modifies the intervention's effect on neonatal body composition.

Substudy 2: impact of the intervention on dietary intake.

A dietary assessment study will be conducted, using a 24-hour dietary recall in a subsample of women. This substudy will enable us to assess possible substitution of the prenatal diet by the BEP supplement.

Substudy 3: impact of the intervention on breastmilk.

Breastmilk samples will be taken in the four study groups to compare the composition and to analyse the interaction between the supplementation periods.

Sample size

With an SGA prevalence of 32% and an anticipated decrease of 7%, a sample of 652 subjects per prenatal arm is required with α=0.05 and β=0.2.[26] To accommodate for possible losses, the number of subjects per arm was increased to 888 (total subjects: 1776). Possible losses are based on previous MISAME studies where the prevalence

Table 2 Secondary outcomes of the RCT on maternal, newborn and child level

Maternal outcomes	Newborn	Child
Total and trimester-specific prenatal weight gain and gestational weight change.	Birth weight (measured within 72 hours after birth).	Weight-for-age Z-score at 6 months of age (WAZ) (and 9 and 12 months on a subsample).
Probable and possible maternal postnatal depression at 2 and 6 months of child age.	Birth length (measured within 72 hours after birth).	Weight-for-length Z-score at 6 months of age (WLZ) (and 9 and 12 months on a subsample).
Maternal anaemia at the third antenatal consultation.	Ponderal or Rohrer's index at birth.	Stunting at 6 months of age.
Women's mean and minimum dietary diversity score (measured twice weekly).	Gestational age at delivery.	Wasting at 6 months of age.
	Large-for-gestational age.	Underweight at 6 months of age.
	Chest circumference (measured within 72 hours after birth).	Duration of exclusive breastfeeding during the first 6 months of age.
	Head circumference (measured within 72 hours after birth).	Incidence of child wasting over first 6 months of life.
	Arm circumference (measured within 72 hours after birth).	Weight gain over first 6 months of life.
	Incidence of preterm birth.	Child mortality (between birth and 6 months of age).
	Fetal loss.	Monthly change in LAZ over first 6 months of life.
	Stillbirths.	Monthly change in WLZ over first 6 months of life.
		Monthly change in WAZ over first 6 months of life.
		Monthly change in head circumference over first 6 months of life.
		Child morbidity symptoms over first 6 months of life.
		Anaemia at 6 months of age.
		Haemoglobin concentration at 6 months of age.

LAZ, length-for-age z-score; RCT, randomised controlled trial.

was ~26 % due to a combination of miscarriage, stillbirths, multifetal pregnancies, outmigrants, maternal deaths and incomplete data.[18] For the analysis of an effect of the postnatal intervention on LAZ at 6 months of age, the minimally detectable effect depends on the presence or absence of an interaction effect between the prenatal and postnatal intervention. In the absence of a statistically significant interaction between prenatal and postnatal intervention, at sample size of 588 children per postnatal study arm would allow us to detect a difference of 0.18 Z-score (SD=1.1) based on a cross-sectional survey conducted in the Gourcy health district in Burkina Faso,[31] between study arms with α=0.05 and β=0.20. This implies that if ~1400 singleton live births are available, we allow for a maximum loss to follow-up of 16%. In the presence of a statistically significant interaction between prenatal and postnatal intervention, a total sample size of 1176 represents 294 children per factorial combination of the prenatal and postnatal study group (four groups in total). A subgroup size of 294 would allow us to detect a difference in LAZ at 6 months of age of 0.28 assuming an SD of 1.1, α=0.025 (Bonferroni correction for two primary endpoints analyses) and β=0.20.

Data collection

Anthropometric and clinical procedures

At enrolment, anthropometric measurements from all women will be taken. Gestational age will be determined during an ultrasound consultation by measuring crown-rump length (7–13 weeks) or by calculating the mean of three to four measurements: biparietal diameter, head circumference, abdominal circumference and femur length (12–26 weeks).[32]

During pregnancy, clinical follow-up will consist of antenatal visits following the national guidelines.

At birth, anthropometric measurements of all neonates will be assessed in duplicate within the first 72 hours of life (in practice, the aim is to measure within the 24 hours of life). After birth, mother and child will visit the healthcare centres monthly for a follow-up on clinical,

Table 3 Participant timeline schedule of enrolment, interventions, assessment and visits

	Enrolment		Allocation	Postallocation: Pregnancy and birth				After birth							
	Start	5-weekly visits	ANC 1	Household visit	Ultrasound	ANC 2, 3 and 4	Birth	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12
Enrolment															
Census	×														
Pregnancy identification		×													
Pregnancy confirmatory test			×												
Informed consent and allocation to study group			×												
Study groups															
Prenatal BEP+IFA			x	—	—	—	x								
Prenatal IFA			x	—	—	—	x								
Postnatal BEP+IFA*							x	—	—	—	—	—	x		
Postnatal IFA							x	—	x						
Assessments															
Mothers															
Baseline questionnaire				×											
Gestational age determination					×										
Skinfold measurements					×										
Weight (kg) and arm circumference (mm) †/‡			×			×	×	×	×	×	×	×	×	×	×
Height (cm)			×												
Haemoglobin (g/dL)			×			× (ANC3)									
Women's Dietary Diversity Score (twice weekly)				×											
Maternal depression			×						×				×		
Infants															
Birth weight (kg)							×								
Birth length (cm)							×								
Head circumference (mm)							×	×	×	×	×	×	×		
Chest circumference (mm)							×								
Arm circumference (mm)							×	×	×	×	×	×	×	×	×
Morbidity								×	×	×	×	×	×		
Mortality							×	×	×	×	×	×	×		
Weight (kg) and height (cm)								×	×	×	×	×	×	×	×

Continued

Table 3 Continued

	Enrolment		Allocation	Postallocation: Pregnancy and birth				After birth							
	Start	5-weekly visits	ANC 1	Household visit	Ultrasound	ANC 2, 3 and 4	Birth	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12
Breastfeeding practices								×	×	×	×	×	×		
Haemoglobin (g/dL)													×		

*The IFA tablets will be given during the first 6 weeks after birth in the postnatal intervention group, according to the national health protocol.
†Only maternal weight will be taken at birth.
‡In a subsample at months 9 and 12.
BEP, balanced energy–protein; IFA, iron/folic acid.

anthropometric and child morbidity measures (signs including fever, vomiting, diarrhoea, cough, difficulty breathing and running nose). A subsample will be measured at the healthcare centres or at home by the project interviewers to collect postnatal data at months 9 and 12.

Haemoglobin concentrations will be measured in women at enrolment and during the third antenatal care visit. This will be conducted at 6 months of age among children.

Baseline questionnaires

Prenatal and postnatal maternal depression will be assessed using the standardised Edinburgh Postnatal Depression Scale questionnaire consisting of 10 questions.[33] Project midwives will be trained for this, and the questionnaire will be asked at inclusion and at months 2 and 6 after birth. Socioeconomic and demographic information from all participants will be collected once included. Trained project interviewers will ask questions on household members' characteristics, household properties, WASH environment and household food security.[34] The women's dietary diversity score will be measured in all participating women by the FA during the home visits. This will be enumerated twice a week per participant using the Women's Dietary Diversity Score with 11 food groups.[35]

Table 3 shows the overview of the time schedule and measurements of the trial.

Quality of all study data will be insured by a thorough training of all field staff. Procedures to handle data collection tools (questionnaires, anthropometric and clinical measurement material, and laboratory procedures) will be pretested in the field during a dry-run of ±3 months. Anthropometric measurement standardisations of the field staff will be repeated bimonthly throughout the trial. Anthropometric measurements will be taken in duplicate. Newborns will be measured within 72 hours after birth (preferably within the 24 hours), and all weighing scales and HemoCue 201+ devices will undergo weekly quality control. A WhatsApp group will be set up where problems can be communicated and solved quickly.

All data collection forms of the trial can be found on: www.misame3.ugent.be

Women will be designated as lost to follow-up if they move from the study area or withdraw their participation. Reasons for discontinuation will be recorded.

Women will be enrolled in the study from October 2019 until the total sample size has been reached.

Data management and analysis

FAs will use smartphones with computer-assisted person interviewing programmed in CSPRO (version 7.3.1) to collect data during household visits. The study data collected by the project medical doctor, project midwives and interviewers will be done by Survey Solutions data entry software (V.19.12.6) on tablets. This data will be uploaded to a central server on a weekly basis. All questionnaires were programmed and have been tested on the Survey Solutions Designer website and include validation codes to promote the quality of the data entry in the field. Assignments will be sent once a week to the tablets of the field team, and preloaded data collected at an earlier contact moment will be used to lower the amount of incorrect data. Paper forms will also be available on the field as a backup.

Further data quality checks will be conducted in Stata V.14.2 (Statacorp, Texas, USA). Missing or inconsistent data outliers will be sent back to the field for revision.

Statistical analysis

We refer to the Statistical Analysis Plan of the trial '*Statistical analysis plan: Impact of a prenatal and postnatal balanced energy-protein supplement on birth size and postnatal child growth in Burkina Faso*' published on: www.misame3.ugent.be

Data monitoring

Data monitoring and auditing

The Data and Safety Monitoring Board is an independent multidisciplinary group whose members are not involved in the trial. The board consists of a Belgian endocrinologist, a Belgian paediatrician, a Burkinabè paediatrician, a Belgian gynaecologist and a Belgian ethicist.

Serious adverse events (SAEs)

FAs will be trained to recognise health issues and will actively refer those participants to see the project midwife in the primary health facilities or Centre de Santé et Promotion Sociale (CSPS) in the event they occur. All SAEs will be recorded on a case-by-case basis, and verbal autopsies will be conducted for maternal, neonatal and infant deaths by the field medical doctor.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

MISAME-III has been reviewed and approved by the University Hospital of Ghent University (B670201734334) and the Burkinabe ethics (N°2018–22/MS/SG/CM/CEI) committee. Important protocol changes will be noted on ClinicalTrials.gov. When eligible women meet the inclusion criteria, project midwives will explain the background and procedure of the complete trial. Written informed consent or assent will be asked from the participating women. In case of illiteracy, a thumb print will be asked and witnessed by the recruiting investigator and one extra witness. Participants will be told that all data collected during the trial is confidential and that they are allowed to withdraw at any time. A copy of the informed consent and assent can be found on www.misame3.ugent.be and as supplementary file (online supplemental file 2).

Patient and public involvement

MISAME-III has been well accepted by the community, because of the previous positive experiences they had with the MISAME-I and II studies. Through the formative study, women were involved in the choice of BEP supplement. Workshops will be planned at the end of the study in order to communicate the study results to the community.

Ancillary care

The MISAME-III project will pay for ancillary care when participants have health issues and in case the costs are not covered by the national healthcare programme. Participants suffering harm due to their trial participation will be covered.

Confidentiality

A data management plan has been put in place to address concerns regarding the General Data Protection Regulation rules. During the trial, the data files containing personal identifying information will be stored on the Survey Solutions server. Only the principal investigators and the project coordinators will be able to access those files.

Dissemination plan

On completion of the trial, all anonymised study data will be available on request. Final results will be communicated to the participants, the Burkinabè Ministry of health, the field staff, the BMGF, Ghent University researchers and students, AFRICSanté, healthcare professionals and other relevant international public institutions. Papers on the study results will be published in peer-reviewed journals and will be available on the project website. All investigators contributing to the realisation of the project and publication of results will be included as an author. Other contributors such as the participants, FA and field staff members will be mentioned in the acknowledgements.

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DISCUSSION

In this paper, the protocol of an individually randomised four-arm efficacy trial in rural Burkina Faso has been described in which pregnant and lactating women in the intervention group will receive a BEP supplement together with IFA tablets. The control group will only receive the standard IFA treatment.

The key features of the present trial are, first, the inclusion of a formative study for a better understanding of which type of supplement is preferred, what taste is most acceptable and which factors affect adherence in the study population. Second, the supplementation will be given during pregnancy and during the first 6 months after birth. This will give us the opportunity to assess the specific value of postnatal supplementation on several outcomes. Third, the observed daily intake of intervention and control supplements is a key feature to ensure compliance and to avoid sharing of the supplements with other household members. Fourth, MISAME-III has the advantage of being the third trial of its kind in the study area. This presents an opportunity to anticipate the issues that arose in previous trials. For instance, women in specific villages tended to leave their homes for a longer period to go work on the fields outside the village. This posed problems in the continuation of the supplementation in the past and will be taken into consideration during MISAME-III. Fourth, four substudies are nested in the main trial that will provide insight into the mechanism by which prenatal BEP supplementation affects birth and infant outcomes. And last, similar studies are being conducted in other countries, allowing for comparison between results from different contexts.

The MISAME-III study will provide evidence on the impact of BEP supplements on birth and infant size using a rigorous study design. The study results will further strengthen and refine WHO's recommendation on the use of context-specific BEP supplementation during pregnancy and lactation.

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Contributors KV wrote the manuscript; PK, LH, CL, NDC, LCT, KV, BdK, TD-C and GHC designed the study and the protocol; PK, LH, LCT, KV and BdK designed the study material tools; LCT, LH, KV, BdK, MO and RG trained the field data collectors; TD-C and GHC critically reviewed and revised the manuscript; all authors contributed substantially to the manuscript and approved the final version.

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Competing interests None declared.

Patient consent for publication Not required.

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REFERENCES

1 Lee ACC, Katz J, Blencowe H, *et al*. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *Lancet Glob Health* 2013;1:e26–36.
2 Katz J, Lee AC, Kozuki N, *et al*. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. *Lancet* 2013;382:417–25.
3 van Rossum CTM, Fransen HP, Verkaik-Kloosterman J, *et al*. *Dutch national food consumption survey 2007–2010: diet of children and adults aged 7 to 69 years*, 2011.
4 Lee AC, Kozuki N, Cousens S, *et al*. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21st standard: analysis of CHERG datasets. *BMJ* 2017;358:j3677.
5 Stevens B, Buettner P, Watt K, *et al*. The effect of balanced protein energy supplementation in undernourished pregnant women and child physical growth in low- and middle-income countries: a systematic review and meta-analysis. *Matern Child Nutr* 2015;11:415–32.
6 WHO. *WHO recommendations on antenatal care for a positive pregnancy experience*. World Health Organization, 2016.
7 Krishna U, Bhalerao S. Placental insufficiency and fetal growth restriction. *J Obstet Gynaecol India* 2011;61:505–11.
8 Mridula D, Mishra C, Chakravorty A. Dietary intake of expectant mother. *Indian J Nutr Diet* 2003;40:24–30.
9 Tang AM, Chung M, Dong K. *Determining a global mid-upper arm circumference cutoff to assess malnutrition in pregnant women*. Food and Nutrition Technical Assistance, 2016.
10 Branca F, Grummer-Strawn L, Borghi E, *et al*. Extension of the WHO maternal, infant and young child nutrition targets to 2030. *SCN News* 2015;41:55–8.
11 Keats EC, Haider BA, Tam E, *et al*. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2019;3:CD004905.
12 Hambidge KM, Westcott JE, Garcés A, *et al*. A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the women first trial. *Am J Clin Nutr* 2019;109:457–69.
13 Ota E, Hori H, Mori R. Antenatal dietary education and supplementation to increase energy and protein intake. *Cochrane Database Syst Rev* 2015;6:CD000032.
14 Imdad A, Bhutta ZA. Maternal nutrition and birth outcomes: effect of balanced protein-energy supplementation. *Paediatr Perinat Epidemiol* 2012;26:178–90.
15 Kramer MS, Kakuma R. Energy and protein intake in pregnancy. *Cochrane Database of Syst Rev* 2003;4.
16 Bill and Melinda Gates Foundation (BMGF). *Framework and specifications for the nutritional composition of a food supplement for pregnant and lactating women (PLW) in undernourished and low-income settings. Expert consultation Seatle, US*, 2016.
17 Roberfroid D, Huybregts L, Lanou H, *et al*. Effects of maternal multiple micronutrient supplementation on fetal growth: a double-blind randomized controlled trial in rural Burkina Faso. *Am J Clin Nutr* 2008;88:1330–40.
18 Huybregts L, Roberfroid D, Lanou H, *et al*. Prenatal food supplementation fortified with multiple micronutrients increases birth length: a randomized controlled trial in rural Burkina Faso. *Am J Clin Nutr* 2009;90:1593–600.
19 United Nations Development Programme. Human development reports [online], 2019. Available: http://hdr.undp.org/en/countries/profiles/BFA
20 Unicef. *The state of the world's children: children with disabilities: UN*, 2013.
21 MEASURE DHS, ICF Macro. *Enquête démographique et de santé et indicateurs multiples (EDSBF-MICS IV), Rapport préliminaire, Burkina Faso, 2010*. Ouagadougou: INSD, 2011.
22 Institut National de la Statistique et de la Démographie (INSD) et ICF International. *Enquête Démographique et de Santé et Indicateurs multiples Du Burkina Faso 2010*. Calverton, Maryland: INSD et ICF International, 2012.
23 MOH. *National iodine status and anemia survey, Burkina Faso*, 2014.
24 MOH. *MdlS. Enquête Nutritionnelle Nationale 2013*, 2013.
25 Savy M, Martin-Prével Y, Sawadogo P, *et al*. Use of variety/diversity scores for diet quality measurement: relation with nutritional status of women in a rural area in Burkina Faso. *Eur J Clin Nutr* 2005;59:703–16.
26 Huybregts LF, Roberfroid DA, Kolsteren PW, *et al*. Dietary behaviour, food and nutrient intake of pregnant women in a rural community in Burkina Faso. *Matern Child Nutr* 2009;5:211–22.
27 Jones L, de Kok B, Moore K, *et al*. Acceptability of 12 fortified balanced energy protein supplements - Insights from Burkina Faso. *Matern Child Nutr* 2021;17:e13067.
28 de Kok B, Moore K, Jones L. Acceptability and at-home consumption of two fortified balanced energy-protein supplements among pregnant women in rural Burkina Faso: a mixed methods study. *Matern Child Nutrit* 2021;17:e13067.
29 Villar J, Altman DG, Purwar M, *et al*. The objectives, design and implementation of the INTERGROWTH-21st project. *BJOG* 2013;120:9–26.
30 de Onis M, Branca F. Childhood stunting: a global perspective. *Matern Child Nutr* 2016;12:12–26.

31 Becquey E, Huybregts L, Zongrone A, *et al*. Impact on child acute malnutrition of integrating a preventive nutrition package into facility-based screening for acute malnutrition during well-baby consultation: a cluster-randomized controlled trial in Burkina Faso. *PLoS Med* 2019;16:e1002877.
32 Salomon LJ, Alfirevic Z, Da Silva Costa F, *et al*. ISUOG practice guidelines: ultrasound assessment of fetal biometry and growth. *Ultrasound Obstet Gynecol* 2019;53:715–23.
33 Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. development of the 10-item Edinburgh postnatal depression scale. *Br J Psychiatry* 1987;150:782–6.
34 Femi A. Perception of performance appraisal and workers' performance in Wema Bank Headquarters, Lagos. *Global J Arts Human Soc Sci* 2013;1:89–101.
35 Martin-Prével Y, Allemand P, Wiesmann D, *et al*. *Moving forward on choosing a standard operational indicator of women's dietary diversity. FAO*, 2015.

Supplementary file : SPIRIT Checklist 2013.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 / 20
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	20

Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7 /
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

1. PARTICIPANT INFORMATION SHEET

THE EFFECT OF BALANCED ENERGY-PROTEIN SUPPLEMENTATION DURING PREGNANCY AND LACTATION ON BIRTH OUTCOMES AND INFANT GROWTH IN RURAL BURKINA FASO

Coordinating Investigator : Prof. Dr. Patrick Kolsteren
Principal Investigator: Dr. Laeticia Celine TOE
Sponsor of the study: Ghent University
Participant Number: |__||__||__||__||__| _ |__||__|

Dear madam,

You are invited to participate in a study that wants to study the effect of providing a food supplement during pregnancy and lactation on the growth of your baby. The study is a collaboration between the Institut de Recherche en Sciences de la Santé (IRSS) and AfricSanté in Burkina Faso, Ghent University of Belgium and the International Food Policy Research Institute (IFPRI) in the USA. Before you decide to participate in this study, it is important that you read/ are read and explained to this form, because it explains your rights and our responsibilities to you. In this information and consent form, the purpose, examinations, advantages, risks and inconveniences related to this study are explained. The available alternatives and the right to withdraw your consent to participate at any time are also described below. No promises or guarantees can be made about the results of the study. You have the right to ask questions at any time, for example about the possible and/or known risks related to this study.

PURPOSE AND DESCRIPTION OF THE STUDY

This research study will provide more evidence and insight into how we can improve pregnancy outcomes , birthweight of babies and the growth of newborns. With this study, we aim to assess whether the provision of the food supplement under investigation can improve the growth of fetuses during pregnancy and that of infants during their first 6 months of life. In addition, we will evaluate how the food supplements that are offered to you improve the nutritional quality of the human milk produced for your child, as well as your and your child's body composition.

We will thus compare the effect of 2 different approaches. One is to give you a tablet during your pregnancy and with the other approach participants will also receive a food supplement next to the tablet. The tablet is what you normally received for any pregnancy according to the guidelines of the ministry of health of Burkina Faso. We will provide the supplement for the entire duration of your pregnancy. After birth some mothers will continue to receive a food supplement for six months. Who receives what is entirely determined by chance. In total, 1776 pregnant women living in the catchment area of the health centers of de Boni, Dohoun, Dougmato II, Karaba, Kari and Koumbia will be recruited to participate in this study.

Vanslambrouck K, *et al. BMJ Open* 2021; 11:e038393. doi: 10.1136/bmjopen-2020-038393

HOW THE STUDY IS DONE

If you are confirmed pregnant and accept to participate in this study, the midwife will do a full medical check-up of you and your baby according to medical standards. She will also inform you about a good dietary practices for you during your pregnancy.
After the check-up we will provide you either with the tablets, or the food supplements.

Thereafter, you will receive a daily visit from the community health worker who will ask you to take the tablet or eat the food supplement. A ultrasound examination will be planned for you within 2 weeks after your first consultation and will be performed by the project doctor. We will also arrange for you regular check-ups of your pregnancy by the midwife or the medical doctor.

EXAMINATIONS IN THE CONTEXT OF THE STUDY

If you accept to participate in the study and if you and your child meet all the conditions for participating in the study, the following tests and examinations will be performed:

- We will take your weight t and height and ask you your age at inclusion.
- The midwife will invite you for antenatal check-ups according to the guidelines of the ministry of health and the medical doctor will perform an echography of your baby. This is not invasive and has no known risks. It is like taking a picture of your baby. As part of the routine check-up we will take fingerpick blood to test whether you are anemic and give you treatment when necessary.
- We will also ask you questions about your mental wellbeing, e.g. how you are living your pregnancy and if something bothers you in your everyday life.
- After delivery we will again take fingerpick blood to test whether you are anemic and give you treatment when necessary.
- When you deliver we will weigh your baby and measure his/her length and head and chest circumferences.
- After birth we will visit you or ask you to come to the health center every month to have the weight and the length of you baby taken. At that time we will also ask you question on illnesses your child might have had in the previous week and on what he/she has been eating.
- We will also perform a finger/heel prick on your baby to see if he/she is anemic and a treatment will be provided if necessary
- Halfway through pregnancy in some of the participating women, we will ask you questions about what and how much they have eaten the day before the interview. This should take about half an hour.

When the doctor identifies a medical problem he will see to it that you receive the appropriate information and necessary treatment, and will refer you when necessary.

If your child suffers from a disease or undernutrition, he/she will be treated in the best way possible. In such case, your child will be referred to the local health center or the district hospital, for further physical examination by a medical doctor.

VOLUNTARY PARTICIPATION

You participate entirely voluntarily in this study. You have the right to refuse to participate in the study. Your decision to participate or not in this study, or to stop your participation in this study will have no influence whatsoever on present and future medical consultations and possible treatments. You also have the right yourself to stop your participation in the study at any time, even after you have signed

this informed consent form. The withdrawal of your consent will not cause any disadvantage or loss of advantages / privileges.

RISKS AND INCONVENIENCES

Finger-prick blood will be taken from you at the first ante-natal consultation. You will experience a prick in your finger, however the prick is not invasive. Antiseptic measures will be taken to prevent any inflammation/ infection of your finger.

The food supplement used in this study is safe for you and your baby. The food supplement contains milk, sugar, oil, peanut butter and a mix of vitamins. Previous studies in Houndé that provided similar food supplements during pregnancy have not documented any complications during pregnancy or delivery. However, the supplement contains milk, which can cause bloating, flatulence and other digestive discomfort in some people. We encourage you to notify us, should you experience these effects, so we can take measures to insure you the best comfort possible.

All other investigation are routinely done as part of the follow-up of pregnancy.

Some of you will be asked to donate a small amount of breast milk at two time points during the study (between 1-2 months and 3-4 months age of your child). This will not diminish the amount of milk for your child or influence lactating performance. We will ask your permission for this donation again when the time comes.

In a random sample of all participants, we will assess body composition after delivery in the mother and the infant, using a special water that has been proven safe for such use. If you are chosen for that examination, we will provide detailed explanations of the procedure to you and a specific consent will be ask before we perform the assessment. Your privacy will be respected at all times

BENEFITS

We expect to show that taking food supplements during pregnancy and lactation will help children grow better and improve the quality of breastmilk. If this would be the case we will have the possibility to change policy to provide supplements to pregnant and lactating women.

PROTECTION OF YOUR PRIVATE LIFE

Your identity and your participation in this study will be treated strictly confidential. The specific information we obtain from you will not be shared with anybody, except the study investigators and partner institutes. Your identity remains secret since your personal information will only be designated by a unique participant number. Your name will not appear in any reports or publication resulting from this study. After the study is completed, you may request information about the study results. As soon as possible (maximum 5 years) after the study is completed, all personal information from participant shall be deleted from all databases to ensure complete anonymity. Those anonymized databases shall be shared with other researchers to advance research on mother and child health. This shall be done in strict accordance with international laws and regulations about privacy.

ETHICS COMMITTEE

Before starting, this study has been reviewed and approved by an independent Ethics Committee in Belgium, namely the Ethics Committee of the University Hospital in Ghent and it has been reviewed and approved by the Ethics Committee Centre Muraz in Burkina Faso. These committees also perform

continuous reviews of the study during its progression to make sure the study is carried out in the safest possible way.

COMPENSATIONS AND INCIDENTS THAT MAY OCCUR IN THIS STUDY

All costs related to sickness occurring during the study will be reimbursed to you. Investigators shall seek to provide a compensation and/or the best possible treatment in the event of damages/ injuries that may occur as a result of your participation in this study. For any other damages thought to be related to your participation in this study, and occuring after the study has been completed, participant may file a complaint to the relevant jurisdiction, which will treated in accordance with applicable laws in Burkina Faso.

CONTACT PERSONS IN CASE YOU HAVE QUESTIONS ABOUT THIS STUDY

If you have any questions concerning your participation in this study, or think you have been injured as a result of the study or have a reaction to the study food, inform the village health worker who visits you. S/he will bring you immediately in contact with the project coordinator or the project doctor. All village health workers have cell phones to contact these persons directly. You may also contact, now, during or after the study:

The principle investigator in Burkina Faso: Dr. Laeticia Celine Toe, Tel : +226 71 00 72 72
The president of the ethic committee: Dr. Adama Dembélé, Tel: +226 20 97 01 02
Or The local project Coordinator : Mr. Moctar Ouédraogo, Tel: +226 70 23 81 98
Or project medical doctor: Compaoré S. Anderson Casimir Tel : +226 70 57 51 02

Informed consent

Before you agree to participate in the informal consensus activity, you need to be aware that:

- This study was presented and cleared by the Ethical Review Board of the Ghent University and the ethics committee of Centre Muraz, Burkina Faso.
- This clearance is not to be taken as an obligation to take part in this study.
- Your participation is only voluntary and will be confirmed by signing this form. If you wish, you can withdraw from this study at any point, even after signing this form; you can withdraw by contacting the researcher (below) through email or telephone. You do not have to motivate or explain the decision of withdrawal. In case of withdrawal, your data already collected will be used to assess study outcomes.
- You can revise your answers to the questions if you wish so.
- Your input will be stored anonymously; researchers not involved in the data collection will not have access to your personal data and name. Anonymized databases shall be shared with other researchers for to advance research on maternal and child health.
- You can contact the researcher or the coordinator of the project at any time if you wish to obtain more information regarding this study
- There are very limited risks related to your participation in this study. Those are mentioned under the section " risks and inconveniences" of the information sheet. However, in accordance with the Directive concerning experiments on humans (07/05/2004), a civil liability insurance has been foreseen in the event of any injury or damage occurring and deemed due to your participation in this study.

Part intended only for the participant

I, the undersigned, _____
(name and surname) confirm that I have been informed about the MISAME-III clinical trial and that I have received a copy of the Participant Information Sheet and a copy of the consent form. I confirm that I have read and / or understood the four pages of the information sheet for participants. The study responsible gave me enough information about the conditions and duration of the study, and the possible risks and disadvantages. In addition, I had enough time to review the information and to ask questions, and I received satisfactory answers.

- I understand that I can terminate my participation in this study at any time after notifying the study responsible and this decision will not cause any inconvenience to me or my child.
- I am aware of the purposes for which the data is collected, processed and used in this study.
- I am ready to give information about my medical history and that of my child, or about any medication taken or participation in another study.
- I voluntarily consent to participate in this study and to cooperate with the required examinations and tests.
- I consent to my data being shared anonymously for the benefit of research and maternal and child health.
- I understand that auditors, employee representatives, the Commission for Medical Ethics or competent authorities may inspect my data in order to verify the information collected. By signing this document, I give permission for this control. At all times my privacy will be respected.
- I understand that the biological samples collected from me and / or my child will be sent to Europe or the USA for analysis, and this in strict respect of my confidentiality.
- I am aware that this study has been approved by an independent commission for medical ethics linked to the University Hospital of Ghent, examined by the Ethics Committee of the Center Muraz in Burkina Faso and that this study will be carried out in accordance with the guidelines Good Clinical Practice Guidelines and the Declaration of Helsinki, established for the protection of people participating in clinical trials.

Signature (or fingerprint) of the participant

_____

In case of minority

Informed consent of the legal representative

I, the undersigned, _____
(name and surname), legal representative of
_____ (name and surname) confirm that I have been informed about the MISAME-III clinical trial and that I have received a copy information sheet for participants and a copy of the consent form. I confirm that I have read and / or understood the 6 pages of the information sheet for participants. The study responsible gave me enough information about the conditions and duration of the study, the procedures, the advantages and possible disadvantages. In addition, I had enough time to review the information and to ask questions, and received satisfactory answers.

- I understand that I can withdraw my consent at any time after having informed the study managers and this decision will not cause any inconvenience to my child / wife / ward or to myself.
- I am aware of the purposes for which the data is collected, processed and used in this study.
- I voluntarily consent to my child / wife / ward participating in this study.
- I understand that auditors, employee representatives, the Commission for Medical Ethics or competent authorities may inspect their data in order to verify the information collected. By signing this document, I give permission for this control. At all times his privacy will be respected.

Date: | ___ | ___ | / | ___ | ___ | / | ___ | ___ | ___ | ___ | (dd / mm / yyyy)

Signature (or fingerprint) of the participant's legal representative

_____

Part intended for the investigator

I, the undersigned, _____ confirm that I have informed, _____
(full name of the participant) and that she has:

Consent to participate in the study ☐
Refused to participate in the study ☐

Reason for refusal (mark not filled in if no reason provided)

_____

_____

Date | ___ | ___ | / | ___ | ___ | / | ___ | ___ | ___ | ___ | (dd / mm / yyyy)

Signature: _____

If the participant is unable to read and / or write, an impartial witness should be present during the consent discussion. After having read and explained the information sheet and the informed consent form to the participant. After she has verbally consented to her participation in the study, and has affixed her fingerprint, the witness should complete the name of the participant, add the date, and personally sign and date the consent form. By signing the consent form, the witness certifies that the information in the information sheet and the consent form have been precisely explained and understood by the participant and that the participant has freely given her consent.

Name and first name (s) of witness:

_____

Signature of witness :

_____

Date: | ___ | ___ | / | ___ | ___ | / | ___ | ___ | ___ | ___ | (dd / mm / yyyy)

Contact Principal investigator

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