**Clinical Trial Protocol**

**Title**

Micronutrient interventions to improve infant neurocognitive development and growth in early infancy.

**Protocol No: 2.0**

**SCC No:** 25071

**Alias**  **The INDiGO Trial** (**I**mproving Infant **N**eurocognitive **D**evelopment and **G**rowth **O**utcomes with Micronutrients)

**Other Number(s)** KCL REMAS # **23914**

**Protocol Version – Date** 3.0 – January 25 2022

**Sponsor** King’s College London (KCL)

London, UK

**Principal Investigator** Dr Sophie Moore

**For the purpose of review at the Scientific Coordinating and Ethics Committee’s in The Gambia, this is not the final version with full signatories from the Sponsor Institute (King’s College London). All sections pending KCL input are highlighted in yellow throughout. All other sections are complete. A final, fully executed version will be submitted as a protocol amendment, prior to the start of the study.**

Signature page

The clinical trial will be carried out in accordance with the protocol, the ICH Harmonised Tripartite Guideline for Good Clinical Practice, <<*insert other regulations if applicable>>*, and in accordance to local legal and regulatory requirements.

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| **Principal Investigator:**  Sophie Moore    *Name* | **Signature:**  **A picture containing text  Description automatically generated** | **Date:**  18th October 2021 |

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| **Sponsor’s representative:**    *Name* | **Signature:** | **Date:** |

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Key roles

For questions regarding this protocol, contact <<*insert name of appropriate MRC staff>>* at MRC << *insert address, email, phone(s), fax, >>*.

|  |  |
| --- | --- |
| **Author(s):** | Dr Sophie Moore |
| **Sponsor’s representative:** | Amy Holton Quality Manager King’s Health Partners Clinical Trial Office King’s College London Email: Amy.Holton@kcl.ac.uk |
| **Chief Investigator:** | N/A |
| **Principal Investigator(s):** | **Dr Sophie Moore** Reader in Global Women and Children’s Health Department of Women and Children’s Health King’s College London London, SE1 7EH Email: Sophie.Moore@kcl.ac.uk |
| **Sub-Investigator(s):** | **Dr Samantha McCann** Research Associate Department of Women and Children’s Health King’s College London London, SE1 7EH Email: [Samantha.McCann@kcl.ac.uk](mailto:Samantha.McCann@kcl.ac.uk)  Dr Ousman Jarjou Research Clinician MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine Fajara The Gambia Email: Ousman.Jarjou@lshtm.ac.uk  **Professor Andrew Prentice** Head, Nutrition Theme MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine Fajara The Gambia Email: Andrew.Prentice@lshtm.ac.uk |
| **Sponsor’s Medical Expert:** | **N/A** |
| **Trial monitor(s):** | **Clinical Trials Support Office**  MRC Unit The Gambia  PO Box 273, Banjul  The Gambia  E-mail: [dct@mrc.gm](mailto:dct@mrc.gm) |
| **Local Safety Monitor:** | **Dr Uduak Okomo** MRC Unit The Gambia  PO Box 273, Banjul  The Gambia  E-mail: [uokomo@mrc.gm](mailto:uokomo@mrc.gm) |
| **Chair of DMC/DMSB:** | **Dr Mainga Hamaluba** Head of the Clinical Trials Unit Nuffield Department of Medicine Centre for Tropical Medicine and Global Health University of Oxford E-mail: mhamaluba@kemri-wellcome.org |
| **Statistician:** | **Prof Greg Fegan** Clinical Trials Unit Swansea University Swansea, UK  Email: g.w.fegan@swansea.ac.uk |
| **External Adviser:** | N/A |
| **Clinical Laboratory/ies:** | MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine.  Children’s Hospital Zurich, Switzerland  USDA Western Human Nutrition Research Centre, Davis, California, USA |
| **Other institutions/ Collaborators:** | Dr Amina Abubakar, Aga Khan, Nairobi, Kenya  Professor Lindsay Allen, USDA Western Human Nutrition Research Centre, Davis, California, USA  Dr Maria Andersson, Children’s Hospital Zurich, Switzerland  Professor Clare Elwell, University College London, London, UK  Dr Sarah Lloyd Fox, Cambridge University, Cambridge, UK  Mr Modou Phall, National Nutrition Agency, The Gambia |
| **Local Ethics Committee** | Gambia Government/MRC Joint Ethics Committee,  c/o MRC Unit, The Gambia,  PO Box 273, Banjul, The Gambia, West Africa |

List of abbreviations

|  |  |
| --- | --- |
| AE | Adverse Event |
| BRIGHT | Brain Imaging for Global Health |
| CRF | Case Report Form |
| DMC | Data Monitoring Committee |
| fNIRS | Functional Near Infrared Spectroscopy |
| GCP | Good Clinical Practice |
| HOME | Home Observation Measure of the Environment |
| ICH | International Conference on Harmonization |
| INDiGO | Improving Infant Neurocognitive and Growth Outcomes with Micronutrients |
| IEC | Independent Ethics Committee |
| KCL | King’s College London |
| LMIC | Low- and middle-income country |
| MMN | Multiple micronutrient |
| MRCG@LSHTM | Medical Research Council Unit The Gambia at London School of Hygiene & Tropical Medicine |
| MSEL | Mullen Scales of Early Learning |
| MUAC | Mid-upper arm circumference |
| N/A | Not applicable |
| PI | Principal Investigator |
| UNIMMAP | United Nations International Multiple Micronutrient Antenatal Preparation |
| WHO | World Health Organisation |

Protocol summary

|  |  |
| --- | --- |
| **Title:** | Micronutrient interventions to improve infant neurocognitive development and growth in early infancy. |
| **Alias :** | The INDiGO Trial |
| **Phase**: | Efficacy trial of micronutrient interventions (Phase III) |
| **Population:** | Pregnant women and their infants from rural West and Central Kiang, The Gambia |
| **Number of participants:** | 690 pregnant women and their infants |
| **Number of Sites:** | Participants will be recruited from across 58 villages. The study will be based at the MRC Keneba field station in Kiang West |
| **Location of Sites (including satellite sites):**  **Trial Duration:**  **- Clinical Phase:**  **- Whole trial:** | 35 villages in Kiang West region  23 villages in Kiang Central region  42 months  48 months (4 years) |
| **Duration for Participants:** | Pregnancy: Week 20 to delivery  Lactation: Delivery to 6 months post-partum  Infancy: Day 8 to 6 months post-partum |
| **Description of Investigational Products:** | **Pregnancy:**  Test: Daily multiple micronutrient capsules (see Appendix I for detailed composition)  Control: No placebo group  **Lactation (mothers):**  Test: Daily multiple micronutrient capsules (see Appendix I for detailed composition)  Control: Daily maltodextrin capsules  **Infants:**  Test 1: Daily micronutrient syrup (low dose, see Appendix I for detailed composition)  Test 2: Daily micronutrient syrup (neuro-nutrient dose – see Appendix I for detailed composition)  Control: Daily flavoured syrup |
| **Objectives:** | The **primary objective** of this proposal is to determine the most efficacious method of micronutrient supplementation in women and infants from a population with high rates of deficiency, to improve nutritional status, neurocognitive development and growth during early infancy (birth to six months of age).  The **secondary objectives** are to:   1. Assess the impact of micronutrient interventions during pregnancy, lactation and infancy on maternal and infant micronutrient status. 2. Assess the impact of micronutrient interventions during pregnancy, lactation and infancy on infant neurodevelopment to 12 months of age. 3. Assess the impact of micronutrient interventions during pregnancy, lactation and infancy on infant growth trajectories across the first 12 months of life. 4. Assess the impact of micronutrient interventions during pregnancy, lactation and infancy on infant morbidity and infant feeding patterns across the first year of life. |
| **Endpoints:** | **Primary endpoint**: infant neurocognitive development using functional near infrared spectroscopy (fNIRS) assessed when the infant is six-months of age.  **Secondary endpoints**:   1. Maternal plasma and breastmilk micronutrient status in samples collected at (plasma) 20 and 36 weeks gestation and 6 months post-partum and (breastmilk) 1 and 6 months post-partum. 2. Infant micronutrient status in samples collected at birth (cord), 6 and 12 months of age. 3. Trajectories of infant cognitive development, integrating fNIRS, eye tracking and behavioural measures at 1, 6 and 12 months of age. 4. Infant growth (weight, length, head circumference, mid-upper arm circumference measured at monthly intervals to allow computation of z-score based growth trajectories). 5. Maternal and infant morbidity and feeding practices (collected weekly to 6 months of infant age and monthly thereafter). |
| **Description of Study Design:** | Five-arm, double blind, individually randomized placebo-controlled efficacy trial of micronutrient interventions to women (in pregnancy and the first six months post-partum) and their infants (from Day 8 to six months of age) in a rural Gambian population.  The five trial arms will be supplementated with multiple micronutrients in (i) pregnancy; (ii) pregnancy and lactation; (iii) pregnancy and infancy; (iv) pregnancy, lactation and infancy (“low dose”); and (iv) pregnancy, lactation and infancy (“neuro-nutrient dose”) (Figure 1). Supplementation in pregnancy and lactation will be in the form of a daily capsule for the mother, or an identical placebo. Supplementation in infancy will be in the form of micronutrient drops (syrup) for the infant, or an identical placebo. Each group will contain 120 mother-infant pairs (total N=600).  From enrolment into the supplementation phase of the trial, pregnant women will be seen at home daily for observed supplementation and weekly for collection of morbidity data. Full antenatal checks will also be made at clinic visits at 20, 28 and 36 weeks gestation. Deliveries will be attended and a maternal and neonatal health check performed by the clinic team within 48 hours of delivery. From day 8 until 6 months post-partum, mother-infant pairs will be visited daily for supplement observation (mothers) and administration (infants). Weekly home visits will continue throughout this phase for the collection of data on maternal and infant morbidity and infant feeding patterns.  Primary outcome assessments will be made when the infants reach six months of age, with follow up and secondary outcome data collected to when the infant reaches 12 months of age, when their participation in the trial will end. |

# Background information and rationale

## Background information

Undernutrition during the early years of life has a harmful and irreversible impact on child development.[1] This is particularly relevant in low- and middle-income countries (LMIC), where one in three children fail to reach their developmental milestones by school-age.[2] Early deficits in neurodevelopment can predict poorer mental health, academic achievement and economic productivity across the lifespan.[3] The first 1000 days of life, from conception to two years of age, has been identified as a critical period for both physical and neurocognitive development and emphasis is now placed on understanding pathways to developmental deficits during this time, so effective interventions can be identified and taken to scale. There remains an unmet need as many of the interventions tested to date have had disappointing or inconsistent impact. These have included trials of combined nutritional supplementation to both mothers and infants (e.g.[4-8]) and, more recently, testing of multiple interventions (e.g. nutrition, water, hygiene and sanitation) introduced simultaneously (reviewed in Humphrey *et al.* [9]).

A common feature has been the absence of any interventions delivered directly to the infant during the first six-months of life. This is especially the case with nutritional interventions, with the exception of studies that have focused on the promotion of exclusive breastfeeding.[10] Recent data from The Gambia has highlighted that high rates of micronutrient deficiencies occur in the first months of life, even among exclusively breastfed infants[11] with growth faltering very early in life (<6 months of age).[12, 13] Further, preliminary data from the BRIGHT[[1]](#footnote-1) study also indicates that, in comparison to a UK population, neurocognitive development among Gambian infants is impacted across this period.[14] Micronutrients are critical for brain development during the first months of life,[15] yet this window of vulnerability is neglected with respect to maternal and child health policies.

For standard antenatal care, WHO policy recommends daily iron-folic acid supplementation alone,[16] although debate persists regarding the additional use of MMN supplements to provide other essential micronutrients.[10] However, with the knowledge that micronutrient stores may become rapidly depleted if supply is not maintained, even supplementation with MMNs to women in pregnancy may not be adequate to ensure sustained maternal or infant micronutrient sufficiency across the post-partum period. Current WHO policy does not include recommendations to supplement women during lactation, and the existing policy on exclusive breastfeeding to six months implies that breastfeeding is sufficient to supply adequate micronutrients over this period, despite acknowledgement of a weak evidence base.[17] Advanced methods for assessment of micronutrient status of breastmilk have highlighted possible deficiencies in critical micronutrients in women with low micronutrient intakes or stores,[18] supporting the need to improve maternal and/or infant status. Providing a stronger evidence base for linked-up policy across the pregnancy-post-partum continuum would ensure the maintenance of micronutrient supply to young infants, improving development at this critical phase of life.

References of literature and data are listed in Section 14.

## Rationale

The INDiGO trial is based on the following rationale:

***Growth faltering trajectories among rural Gambian infants are ‘set’ before six months of age and infants born at the start of the annual rainy/lean season are especially vulnerable:*** Inlongitudinal studies, we have shown that infants who experience growth faltering in the first six months of life are at greater risk of stunting across childhood [13] and that growth faltering episodes in the first six-months have greater consequences on longer-term growth trajectories than faltering episodes occurring after this time. Infants born at the start of the annual rainy (lean) season are especially vulnerable.[13] The observation that growth faltering in infants <6 months of age has a more detrimental impact on longer term growth trajectories than later faltering has now been replicated through integration of data from 34 longitudinal cohorts (n=95,794 children, ages 0-24 months) in low- and middle-income countries.[19]

***Biomarkers of early brain development show developmental delays in Gambian infants <6 months of age, with longer-term neurocognitive consequences*:** Research on infant brain development in LMICs has been limited by the absence of robust and objective methodologies, and often relies on behavioural observations as proxy measures. As these assessments are unreliable in young infants, identification of early cognitive deficit and windows for targeted intervention has been difficult. Through our Global fNIRS collaboration (https://www.globalfnirs.org/) we have recently implemented functional Near Infrared Spectroscopy (fNIRS) - a non-invasive optical brain imaging method developed for evaluating early infant brain development in the first few months of life [20, 21] - in rural Gambia [22, 23] and shown in the ongoing BRIGHT study an early deficit in development compared to a UK cohort.[14] These findings support the use of early biomarkers of brain development as robust indicators of neurodevelopmental delays.

***Exclusive breastfeeding to six months of age in rural Gambia does not protect infants from growth faltering****:* WHO recommends exclusive breastfeeding for the first 6 months of life, with continued breastfeeding up to 2 years of age, or beyond, along with nutritionally adequate, safe and appropriate complementary foods.[24] Optimal breastfeeding practices unequivocally have short-term advantages for child morbidity and mortality, especially in LMICs,[25] but there are limited studies on infant growth in such settings[12] and the few available show little benefit.[26, 27] In many LMICs, infants are small at birth, show catch up growth in the first few months of life, and then enter a period of reduced growth velocity, resulting in substantial growth faltering by the second year. In a large, contemporary cohort of infants in rural Gambia we have shown that this pattern is not altered by breastfeeding status, and close adherence to WHO policy on exclusive breastfeeding does not prevent growth faltering in this context.[12]

***Even with MMN supplementation across pregnancy, maternal and infant stores of many micronutrients are rapidly depleted post-partum if supply is not maintained:*** In addition to evidence that growth faltering starts very soon after birth and that the prevalence is much higher during the first six months than previously assumed,[28] the limited data available reveal a high prevalence of micronutrient deficiencies in 6-month old exclusively or predominantly breastfed infants.[29, 30] Many breastmilk micronutrients are reduced in populations where diets are habitually poor,[31] with adverse effects reported on infant health and development.[32] Our data from The Gambia shows that supplementation with MMN across pregnancy improves maternal status, but that rapid depletion occurs across lactation, with parallel decreases in breastmilk quality and infant status.[11]

Together, this evidence base provides the support for and rationale behind the hypothesis underpinning the proposed trial that early post-natal nutritional interventions will improve infant neurocognitive development and growth among populations at risk of maternal micronutrient deficiency.

## Potential risks and benefits

The potential risks to human subjects and known benefits, if any, are summarised in Section 11 “Ethical considerations”.

# Study objectives

The **primary objective** of this proposal is to determine the most efficacious method of micronutrient supplementation in women and infants from a population with high rates of deficiency, to improve nutritional status, neurocognitive development and growth during early infancy (birth to six months of age).

The **secondary objectives** are to:

1. Assess the impact of micronutrient interventions during pregnancy, lactation and infancy on maternal and infant micronutrient status.
2. Assess the impact of micronutrient interventions during pregnancy, lactation and infancy on infant neurodevelopment to 12 months of age.
3. Assess the impact of micronutrient interventions during pregnancy, lactation and infancy on infant growth trajectories across the first 12 months of life.
4. Assess the impact of micronutrient interventions during pregnancy, lactation and infancy on infant morbidity and infant feeding patterns across the first year of life.

## Study endpoints

The **primary endpoint** of this study will be infant neurocognitive development using functional near infrared spectroscopy (fNIRS; see Section 5.1.3).

Further **secondary endpoints** relating to each secondary objective outlined above are:

1. Maternal plasma and breastmilk micronutrient status in samples collected at (plasma) 20 and 36 weeks gestation and 6 months post-partum and (breastmilk) 1 and 6 months post-partum (linked to secondary objective 1).
2. Infant micronutrient status in samples collected at birth (cord), 6 and 12 months of age (linkd to secondary objective 1).
3. Trajectories of infant cognitive development, integrating fNIRS, eye tracking and behavioural measures at 1, 6 and 12 months of age (linked to secondary objective 2).
4. Infant growth (weight, length, head circumference, mid-upper arm circumference at monthly intervals to allow computation of z-score based growth trajectories) (linked to secondary objective 3).
5. Maternal and infant morbidity and feeding practices (linked to secondary objective 4).

# Study design

## Type of study and design

Five-arm, double blind, individually randomized placebo-controlled efficacy trial

## Randomisation and blinding procedures

### Randomisation

At the point of enrolment in pregnancy mothers will be randomised to 1 of the 5 study arms, using block randomisation, according to an automated computer-generated randomization scheme. Mothers and their infants will remain in the same group through the duration of the trial.

### Blinding / Emergency unblinding

To ensure blinding to both research staff and study participants, the intervention and control products will be packaged in identical packaging, and pre-randomised using a numerical code.

For women (who will receive intervention or control capsules from enrolment at 20 weeks gestation through to six months post-partum) the intervention and control products will be in the form of an identical looking and tasting daily capsule.

For infants (who will receive intervention or control syrups from Day 8 to 6-months of age) the intervention and control products will be in the form of an identical looking and tasting syrup.

Emergency unblinding will be carried out only on the grounds of patient safety i.e. if the patient’s future clinical treatment or safety requires knowledge of the treatment assignment. The investigator will have the primary right to break the blind in any moment in case of emergency and the investigator will have direct and immediate access to the treatment allocation, and therefore able to unblind immediately and without delay in case of emergency. Treatment allocation details will be assigned and held by an independent member of staff at the MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine. In the event that emergency unblinding is required, the treatment details of the individual patient will be provided to the investigator team.

## Sub-studies

Not applicable.

## Investigational products

### Description of products

**Pregnancy:**

Test: Daily multiple micronutrient capsule (see Appendix I for detailed composition)

Control: No placebo group; all participants receive the test capsules (see Section 11.1.2 for justification).

**Lactation (mothers):**

Test: Daily multiple micronutrient capsule (see Appendix I for detailed composition)

Control: Daily maltodextrin capsules

**Infants:**

Test 1: Daily micronutrient syrup (low dose, see Appendix I for detailed composition)

Test 2: Daily micronutrient syrup (neuro-nutrient dose – see Appendix I for detailed composition)

Control: Daily flavoured syrup

### Formulation, packaging and labelling

**Pregnancy and Lactation**: The multiple micronutrient and placebo products supplied to women across pregnancy and lactation will be supplied as capsules, and packaged in plastic pots providing a 28 day supply. The formulation of the multiple micronutrient test product is a standard formulation, as developed by UNICEF/WHO/UNU for use in pregnant and lactating women globally.[33]

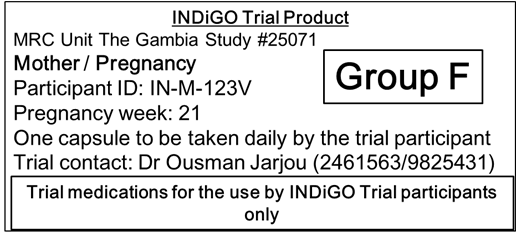
**Infancy**: Infant syrups (test and control) will be packed in glass bottles supplied with a calibrated oral syringe.

Section 11.1.2 details all the safety considerations of the trial products.

All trial products will be labelled following a similar pattern (see mockup provided), distinguished according to whether they are for mothers during pregnancy or lactation or for infants and in accordance to the local regulatory requirements. Information included on each label will be:

Trial name and reference: enabling identification of the trial, site, PI and sponser

Product recipient: Mother / Pregnancy or Mother / Lactation or Infant

Participant ID: A 7 digit code consisting of 3 components (INDiGO Trial code (IN), followed by ‘M’ or ‘C’ to distinguish mother from child, followed by a 4 digit ID (3 numbers and a check letter), e.g. IN-M-123V and IN-C-123X.

Week of study: For mothers in pregnancy, this will be weeks of pregnancy, for mother in lactation, this will be weeks’ post-partum and for infants this will be infant age (in weeks).

Directions for use and trial contact details will be specified on the labels and batch numbers and expiry dates will be printed directly onto the supplement containers at the point of manufacture.

Group: Each of the 5 arms of the trial will be randomly allocated three letters (e.g. Arm 1, F, B T; Arm 2 Z, C, P etc.). Trials products will then be labelled accordingly; so a mother infant pair allocated to Trial Arm 1 all trial products (pregnancy, lactation, infants) will have the same letter (e.g. F, B or T, as per the example above).

### Product storage and stability

To the point of monthly distribution, all products will be stored on the MRC Keneba camp at room temperature (20-25oC) and away from direct sunlight. All investigational products (maternal capsules and infant syrups) are stable when stored at this temperature. The maternal capsules have a shelf life of 24 months and the infant syrups have a 12 month shelf life. Repeat orders will ensure all products are supplied in time, while only using products with a valid expiry date. Expiry dates will be carefully checked by the field coordinator prior to administration to participants.

### Dosage, preparation and administration of investigational products

**Pregnancy and lactation**: The test and placebo capsules will be prepared as a daily dose. Women will be visited daily by a member of the study field team for observed supplementation.

**Infancy**: Infant test and control syrups will be prepared in bottles containing a monthly supply and the required dose will be given to each infant daily, using a graduated oral syringe. The syrup has been manufactured so that a 5mL dose per day provides the daily amount of test micronutrients.

### Concomitant medications/treatments

None applicable, although pregnant women will be encouraged to seek routine antenatal care throughout the duration of their pregnancy.

# Selection and withdrawal of participants

## Selection of participants

Women, resident in the study villages and identified as pregnant (at antenatal clinics and through demographic surveillance), will be invited to participate in the study. Enrolled women will then be invited to the MRC Keneba clinic for an ultrasound examination by the study midwife. Women with an ultrasound-confirmed singleton pregnancy, < 20 weeks gestation will then be enrolled into the trial, and randomized to trial arm. The trial will enroll up to 138 women per trial arm (690 total) with the aim of having 120 infants per trial arm (600 total) at the point of the primary outcome.

## Eligibility of participants

Participants must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the trial.

### Inclusion criteria

* Pregnancy < 20 weeks at initial pregnancy confirmation
* Singleton pregnancy
* Healthy, with no evidence of current severe anaemia
* Willingness to take a daily trial product (capsule) daily from 20 weeks of pregnancy until six-months post-partum and for their infant to receive a daily trial product (syrup drops) from Day 8 until 6 months of age
* Intention to remain resident in West or Central Kiang until the infant is 12 months of age
* Able to provide written informed consent to participate

### Exclusion criteria

Exclusion criteria during the pregnancy phase of the study will include:

* Multiple pregnancy
* Pregnancy ≥20 weeks gestation
* Severe anaemia (<7g/dL)
* Any known history or evidence of chronic disease (including HIV, TB, non-pregnancy-induced-hypertension or diabetes). Women will be offered HIV Voluntary Counselling and Testing (as part of routine antenatal care) and, where positive, excluded from the trial
* Unwilling to avoid the ingestion of other micronutrient supplements during the study period
* If the primary language of the mother is not Mandinka or Fula

Exclusion criteria during the post-partum / infancy phase of the study will include:

* Very or extremely preterm infants (< 32 weeks gestation at delivery)
* Very low birth weight infants (<1.5kg at delivery)
* Infants identified at any follow up point as having severe-acute malnutrition (weight-for-height z score of <-3SD)
* Non-breastfeeding mother-infant pairs
* Unwilling to avoid the ingestion of – or for their infant to avoid the ingestion of – other micronutrient supplements during the study period
* Any condition of the mother or infant that, in the opinion of the investigator, might compromise the safety or well-being of the participant or compromise adherence to protocol procedures (including the identification of severe neurodevelopmental conditions, such as cerebral palsy)

## Withdrawal of participants

A study participant will be discontinued from participation in the study if:

* Any clinical significant adverse event (AE), laboratory abnormality, intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
* Development of any exclusion criteria.

For further details on participant’s premature termination see corresponding section below.

Participants are free to withdraw from the study at any time without giving a reason.

# Study procedures and evaluations

For an overview see annex “Schedule of Events”.

## Study schedule

### Screening

Eligible pregnant women will be identified through antenatal clinics and demographic records. At screening, mothers will have the full purpose of the study explained to them and, following written informed consent, enrolled mothers will be invited to have an ultrasound examination for the confirmation and dating of their pregnancy. Women identified as healthy and with a singleton pregnancy, <20 weeks gestation will be invited back for a further enrolment (baseline) visit at the point they reach 20 weeks (± 7 days) gestation.

### Enrolment (Baseline)

At 20 weeks (± 7 days) gestation, all women will be invited to the MRC Keneba clinic for an enrolment assessment. At these visits, each woman will receive a further ultrasound examination where fetal biometry will be recorded and a standard antenatal care examination (blood pressure, haemoglobin assessment and urinary analysis) performed. Maternal anthropometry (weight, height, head circumference, mid-upper arm circumference) will also be measured and a blood and urine sample collected and biobanked. If confirmed eligible by a clinician, antenatal supplementation will commence after this visit.

### Follow-up

**Pregnancy phase**

Daily supplementation: Following the 20 week (up to 7 days thereafter) clinic visit, women will be visited in their villages daily for observed supplementation (one capsule per participant per day).

Weekly morbidity: Once per week (+ 3 days), maternal morbidity data will be collected.

Clinic visits: Women will be invited for further antenatal clinic visits at 28 (± 7days) and 36 (± 7 days) weeks gestation. The same assessments as performed at the 20 week visit will be made.

**Delivery and neonatal examination**

A system of village assistants will be put in place (one village assistant per study village) to enable early notification to the study team as soon as a woman goes into labour. Following delivery, study field assistants will aim to collect a sample of cord blood and transport it to the Keneba laboratory. The study midwife or clinical delegate will aim to visit the mother and neonate within 72 hours of delivery for a maternal and neonatal health examination and the measurement of neonatal anthropometry (weight, length, head circumference, mid-upper arm circumference). In recognition that a number of women may travel outside of the region to deliver, visits that occur up to 10 days post-partum will still be accepted within the protocol. An eligibility check to proceed into the post-partum supplementation phase will be conducted at this point.

**Post-partum / infancy phase**

Daily supplementation: From Day 8 until 6 months post-partum, mother-infant pairs will be seen daily for supplement administration. For women, supplementation will be observed (by field assistants) and for infants, field assistants will administer the syrup directly. Only where 5 or more consecutive daily visits are missed will this constitute a protocol deviation.

Weekly/monthly morbidity and feeding questionnaire: From week 1 to week 7 months of infant age, data will be collected weekly (and up to 3 days beyond the scheduled visit) on maternal and infant morbidity and infant feeding practices. From 7 to 12 months, this will move to monthly (e.g. one month following the cessation of supplementation, and up to 7 days beyond the scheduled visit).

Monthly home visits: At monthly (± 7 days) home visits until 12 months post-partum, infant anthropometry will be recorded and stool samples collected (for the visits at 1, 6 and 12 months post-partum, these assessments will take place as part of the clinic visits, rather than at home – see below). When the infant is three months of age, the mother will be asked to provide a 10mL of breast milk. At the home visit when the infant is 6 and 12 months of age, we will conduct a Home Observation Measure of the Environment (HOME), which includes 90 minute observation of the infant’s ‘normal’ home life including organization of the home environment, parental involvement in care, variety of daily stimulation and appropriate play materials.[34]

Clinic visits: At 1 (+14 days), 6 (± 14 days) and 12 (± 14 days) months post-partum, mother-infant pairs will be invited to MRC Keneba for a study visit. At all visits, maternal and infant anthropometry will be measured and a 10mL sample of breast milk will be collected from mothers. When the infant is one month of age, a finger prick blood sample will be collected from each infant and a 7.5mL sample of venous blood from mothers and at 6 and 12 months further samples of maternal (7.5mL) and infant blood (5mL) will be collected.

Infant neurocognitive development will be evaluated at each of these clinic visits.

At the one month visit we will assess infant behaviors and reflexes, using a behavioral assessment (Mullen Scales of Early Learning; MSEL) previously adapted for this population and implemented in the BRIGHT study.[35] In addition, we will assess habituation and novelty detection using fNIRS technology.

At the six and 12 month visits we will repeat the measures conducted at 1 month of age (MSEL) and include additional measures of infant attention. Attention is the foundation for learning and the most rapidly developing cognitive domain between birth and 6 months of age.[36] Therefore, building on experience from the BRIGHT study, we will implement age-appropriate measures of visual and auditory attention, using fNIRS and eye tracking technology.

### Final study visit

The final study visit will be conducted when the infant reaches 12 months (± 14 days) of age (approximately 6 months following the completion of the intervention phase of the study). At this visit, infant neurodevelopment will be assessed, maternal and infant anthropometry collected, a sample of blood collected from mothers and infants, and a sample of breast milk collected from mothers, as described above.

### Early termination visit

An early termination visit may occur in this study because of a participant’s voluntary withdrawal, trial team decision or at the discretion of the Data Safety Monitoring Board as described in Section 7. Apart from the safety evaluations, no other evaluations required for the final study visit will be done.

### End of trial definition

The trial end will be defined as the last visit for the last participant.

## Study evaluations

The proposed trial is an efficacy trial of micronutrient interventions to mothers (in pregnancy and lactation) and their infants (across the first six-months post-partum). The Primary Outcome is infant neurodevelopment at six months of age and Secondary Outcomes include infant growth and neurodevelopment to 12-months of age and maternal and infant micronutrient status. The full list of evaluations is as detailed in the “Schedule of Events”.

### Clinical evaluations

Clinical evaluations will include:

**Mothers:** A clinical history (collected by study staff) will ascertain any known history of known chronic disease, including HIV, TB and non pregnancy induced hypertension and diabetes. Blood samples collected at this visit will additionally be used to measure hemoglobin concentration to asses for anaemia. Any woman with a haemoglobin of <7 g/dL will be excluded from the trial, and offered treatment. HIV Voluntary Counselling and Testing will be offered to all women, and serum sample screened as per existing antenatal care guidelines. Urinary analysis will also be performed at antenatal care visits, but will not be used to screen women from the study; women requiring follow up clinical assessment will be reviewed by the study midwife/clinician. Additional clinical assessments will include maternal anthropometry (weight, height (measured at first visit only), mid-upper arm circumference) at each antenatal and post-natal assessment. Further, weekly morbidity questionnaires (collected as part of the routine surveillance during the supplementation phase of the trial) will provide a further clinical evaluation of all study participants.

**Infants**: As part of the trial outcomes, infants will be assessed for neurodevelopment at 1, 6 and 12-months of age. Any infant presenting with obvious signs of clinical delay will be referred to the study clinician, and withdrawn from the trial and referred for follow up if the developmental delay is confirmed clinically. Monthly anthropometry (weight, length, mid-upper arm circumference and head circumference) will also be collected and growth monitoring practiced through use of the infant’s ‘road to health’ card. Infants identified as severely malnourished (weight-for-height z-score < -3 SD) will be withdrawn and provided with nutritional counselling.

### Laboratory evaluations

Laboratory evaluations will include:

**Mothers**: Blood samples (7.5mL) collected at 20, 28 and 36 weeks of pregnancy and at 1 and 6 months post-partum will be processed (including initial assessment of haemoglobin levels, see 5.2.1 above) and samples of plasma/serum frozen and biobanked for subsequent analysis. Planned assessments include the measurement of nutritional biomarkers including the assessment of iron and inflammation status markers (to be performed at MRC Keneba) and B12 and choline (to be shipped to the US for measurement). At these visits, a spot urine sample will be collected from each participating mother for urine analysis (dipstick), as part of routine antenatal care, and an aliquot of urine frozen and stored for shipment to Switzerland and analysis of iodine status biomarkers. At 1, 3, 6 and 12 month’s post-partum, women will be asked to hand-express a sample of breast milk (up to 10mL). These samples will be separated into smaller aliquots and frozen for subsequent shipment to partner laboratories in the US and Switzerland for analysis of nutritional biomarkers.

**Infants**: Blood samples (cord blood, fingerprick at one-month and 5mL at six- and 12-months post-partum) will be processed and samples of plasma/serum frozen and biobanked for subsequent analysis. The same biomarkers as indicated for mothers’ samples (above) will also be made on infant samples. Infant thyroglobulin will be measured in infant blood samples as an indicator of iodine status, as urinary iodine levels are not a robust indicator of infant status. Infant stool samples will be processed into smaller aliquots and biobanked for future use.

# Safety considerations

This trial will be overseen by a Data Safety Monitoring Board (DSMB).

The DSMB will be responsible for reviewing:

* + The trial protocol (before the trial is started).
  + All interim data from the trial (reviewed six-monthly from point of first intervention administered).
  + Treatment safety and efficacy including the protection of the rights and well-being of the participants.
  + The overall progress of the study.

The DSMB will additionally review all Serious Adverse Events (SAEs).

In addition to the DSMB, an independent Local Safety Monitor (Dr Uduak Okomo) will regularly review all AEs and SAEs. This review will focus particularly on AEs causality and reasons for losses to follow up, raising any concerns or issues that present immediate safety concern with the PIs for reporting to the DSMB, while protecting the confidentiality of the trial data and the results of monitoring.

All deaths whether assessed to be related to the IP or not and SAE's suspected to be related to the study supplements will be reported within seven calendar days of receiving the report to the Medicines Control Agency.

## Methods and timing for assessing, recording, and analysing safety parameters

### Adverse events

This study will be conducted according to Good Clinical Practice (GCP) principles.

An Adverse Event (AE) is defined as any untoward or unfavourable medical occurrence in a human subject, including signs and symptoms which are temporarily associated with the individual’s participation in the research, whether considered related to the individual’s participation in the research or not. During the pregnancy phase of the study, women will be administered a weekly morbidity questionnaire and this will be used to collate data on any potential adverse event. During the post-partum / infancy phase of the study, a morbidity questionnaire will be administered weekly and used to collate data on any AE pertaining to themselves or their infant. This data will be captured electronically, and weekly reports compiled for review by the PI or delegate. There are no expected serious or moderate AEs associated with this study. However, a Study Specific Procedure will be drawn up to detail those symptoms that are more likely to be due to the intervention (e.g. gastrointestinal discomfort, diarrhoea), and those that are likely unrelated (e.g. infection-related symptoms). This process will continue after the end of supplementation for a further 4 weeks. In the unlikely case of an AE the field assistants will immediately call the study coordinator to liaise with the a member of the study’s clinical team (midwife, nurse or clinician) as to whether a clinic referral is required. All symptoms or signs reported or observed will be documented as an AE after evaluation by the study nurse or clinician. Any serious AE will be reported according to SOP-CTS-009 and followed up by study personnel until resolved or considered stable.

### Reactogenicity

None.

### Serious adverse events (SAEs)

A Serious Adverse Event (SAE) is any AE that is life-threatening or results in death or requires hospitalisation or prolongation of hospitalisation or is a persistent or significant disability/incapacity. All SAEs will be investigated by the study Research Clinician.

## Reporting procedures

An investigator will assess and document the severity or intensity of the AEs and laboratory changes as follows:

|  |  |
| --- | --- |
| **Grade** | **Description** |
| Mild | Awareness of sign or symptom, but easily tolerated |
| Moderate | Enough discomfort to cause interference with usual activity |
| Severe | Incapacitating with inability to work or do usual activity |
| Life-threatening | This grade will be considered as a SAE |

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on the outcome or criteria defined under the SAE definition. An event can be considered serious without being severe if it conforms to the seriousness criteria; similarly, severe events that do not conform to the criteria are not necessarily serious. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. The PI/study coordinator will report all SAEs without filtration, whether related to the intervention, within 24 hours of becoming aware of the event to the DSMB and Local Safety Monitor and within 3 working days to the Sponsor. If the SAE is related to the intervention, the joint Gambian Government / MRC Joint Ethics Committee will be notified within seven calendar days if fatal or life-threatening, and all others within 15 calendar days. All deaths will be reported to the GG/MRC Joint Ethics Committee at the next scheduled EC meeting. SAEs related to the study supplements and all deaths within 7 calendar days of receiving the report will be reported to the Medicines Control Agency.

The minimum information required for this initial SAE report is:

* + Trial number and (short) title.
  + Participant’s ID (with a clear indication if this is a mother or infant).
  + Nature of the event.
  + Reporter’s name.

The PI/study coordinator will not wait for additional information to fully document the event before reporting. This initial report must be followed by a completed SAE Report within 2 working days, where possible, detailing relevant aspects of the SAE in question. All actions taken by the PI/study coordinator and the outcome of the event must also be reported immediately. For documentation of the SAE, any actions taken, outcome and follow-up, a SAE Report Forms will be used. All follow-up activities must be reported, if necessary, on one or more consecutive SAE report forms in a timely manner. All fields with additional or changed information must be completed and the report form should be forwarded to the Gambia Government /MRC Joint Ethics Committee and the MCA within seven calendar days after receipt of the new information. Hospital case records and autopsy reports, including verbal autopsy, will be obtained where applicable.

## Safety oversight

Safety oversight will be provided by the Local Safety Monitor (Dr Uduak Okomo) who will provide independent advice. Additional oversight and support will be provided by the trial’s Data Safety Monitoring Board (DSMB). Throughout the duration of the trial, the Local Safety Monitor will provide a monthly review of all AEs and SAEs. This review will focus particularly on AE’s causality and reasons for losses to follow up, raising any concerns or issues that present immediate safety concern with the named investigators for reporting to the medical expert, while protecting the confidentiality of the trial data and the results of monitoring.

# Discontinuation criteria

## Participant’s premature termination

Participants have the right to withdraw from the study, or to withdraw their infants, at any time without giving a reason and this will not affect the medical care that would normally be received. The study team may also withdraw a participant from the study if deemed necessary at any time documenting the reason as one of the following:

* + Serious Adverse Event.
  + Adverse Event.
  + Participant’s consent withdrawal.
  + Migrated/moved from the study area.
  + Lost to follow-up.

A 'lost to follow-up' is any participant who completed all protocol specific procedures up to the administration of the investigational product or intervention, but was then lost during the follow-up period, with no safety information and no efficacy endpoint data ever became available.

In case the participant decides to withdraw participation or consent during the study, or to withdraw their infant, we will not work on participant’s samples without permission, but any information already generated from the samples until the time of withdrawal will be used and samples already collected, for which they have given consent, will also be analysed and data used. The study clinician may also ask for tests for the participant’s safety only. The PI/trial coordinator will ask about the reason for any withdrawal and request follow-up with the participant regarding any unresolved AEs for particpant’s safety. For withdrawn participants no study specific data will be collected.

## Study discontinuation

A Data Safety Monitoring Board will oversee safety. The rules for study termination will be set by the DSMB at their first meeting.

# Statistical considerations

The **primary research hypotheses** we will test in this trial are:

1. Maternal supplementation with multiple micronutrients (MMN) across pregnancy and lactation confers greater benefit to infant brain development than supplementation in pregnancy alone.
2. Direct supplementation of MMN to infants from birth to six-months of age, alongside breastfeeding, confers greater benefit to infant brain development than indirect supplementation to the mother across pregnancy and lactation.
3. A tailored ‘neuro-nutrient’ MMN supplement targeted to infants will out-perform the standard formulation of MMN with respect to infant brain development.

We used BRIGHT habituation data from 150 Gambian infants at five months for power calculations.[14] A five-arm trial is proposed (see Schematic of Study Design, Page 30) with 120 mother-infant pairs required to provide adequate power to support the trial’s primary hypotheses.

With a mean (standard deviation, SD) of 0.06(0.51)µM, 120 mother-infant pairs per arm has 95% power to detect a 0.5 SD difference in response at P<0.05. We used a penalised alpha (0.015) in our design to allow for multiple comparisons at the 0.05 threshold for analysis. A 15% attrition to 12 month post-partum requires 138 women per arm to be enrolled in pregnancy.

Analysis will be by arm allocated using least squares multiple regression models. Per protocol analyses will further investigate the potential effectiveness of these interventions. Adjustment for factors unbalanced across arms at baseline will be made. We will explore the combination (interaction) of treatment effects but have not powered the study on this. However, given our ability to look at three comparisons we believe this is a reasonable compromise. Formally detecting a 2x2 interaction effect requires at least 4 times the sample size for a single factor whereas we are suggesting a 3-fold inflation for three separate tests i.e. Arm 1 versus arm 2, Arm 3 versus Arm 4 and Arm 4 versus Arm 5 (the latter being powered as a one-sided superiority test).

The Data and Safety Monitoring Board (DSMB) will be responsible for reviewing participant safety data throughout the duration of the trial. For the purpose of trial monitoring, group differences in morbidity reports and adverse events from mothers and/or infants will be compared. Additional data that will allow for comparisons of safety among the treatment (active and control) groups will also be provided to the DSMB, including treatment retention and reasons for participant drop out.

# Data handling and record keeping

## Data management and processing

Two types of data will be collected; Quantitative (e.g. infant size) and qualitative (e.g. supplement adherence data) collected directly into study specific CRFs and imaging data, collected directly from the fNIRS/eye tracking system and downloaded directly to the server. Data from both sources will be linked using the participant ID number, which will be a unique number allocated at consent into the trial.

All quantitative and qualitative data will be collected into a trial-specific RedCap database. CRFs will be accessed via benchtop computers on the MRC Keneba camp or capsules in the field / at the site of data collection. Where there is internet connectivity, collected data will be stored directly into the central server on the MRC Keneba camp. Where there is no/unreliable internet connectivity, data will be stored locally on the capsule and later (within 24 hours of collection) synchronized to the server.

Prior to the start of the trial, all project staff will be trained on study data collection and handling. Training will be documented. Only staff who have been trained will be able to access and complete study CRFs. To ensure standardization of processes, standard operating procedures will be used, and principles of good clinical practice will be adhered to throughout. To help ensure data quality, data entry screens will be designed with range checks, skip patterns and validations, where appropriate. Mandatory field checks and other computable data (e.g. dates of visit) will be prepopulated to eliminate errors. The study Data Manager will conduct regular data cleaning routines to flag data queries that were not picked up at earlier stages. All data queries will be answered in writing by a senior member of the study team involved in the generation of the data (e.g. clinical team, lab team, field team, or neurodevelopment team) normally within one week.

## Source documents and access to source data

The Principal Investigators will maintain appropriate medical and research records for this study in compliance with the principles of good clinical practice and regulatory and institutional requirements for the protection of confidentiality of participants. The source document for related study data will be listed in a designated source document log. The study team members will have access to records.

The authorised representatives of the sponsor, the ethics committee(s) or regulatory bodies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

## Protocol deviations

A protocol deviation (PD) is any noncompliance with the clinical trial protocol, good clinical practice (GCP), or other applicable regulatory requirements. The noncompliance may be either on the part of the participant or the investigator including the study team members, and may result in significant added risk to the study participant. As a result of a deviation, corrective actions will be developed and implemented promptly.

If a deviation from, or a change of, the protocol is implemented to eliminate an immediate hazard(s) to trial participant without prior ethics approval, the PI or designee will submit the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) as soon as possible to the sponsor for agreement and the relevant independent ethics committee (IEC) for review and approval.

The PI or designee will document and explain any deviation from the approved protocol on the CRF, where appropriate, and record and explain any deviation in a protocol deviation form that will be maintained as an essential document and report all major deviations to the Sponsor and ethics committee within 7 days.

# Quality control and quality assurance

## Study monitoring

The study may be subject audit by King’s College London under their remit as sponsor, the MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine under their remit as host institute, or by other regulatory bodies to ensure adherence to GCP.

Risk-based trial monitoring will be conducted by the designated monitor of the MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine Clinical Trials Support Office in keeping with the approved monitoring plan. The monitoring of study will follow the Unit’s SOP-CTS-005 on Monitoring (available on request). An initiation visit will occur, and formal study start approval obtained from the Sponsor, KCL, before the start of recruitment. Interim visits will be conducted during the conduct of the study in line with the monitoring plan. At the end of the study, a close out visit will be conducted after last participant last visit and database cleaning completed and ready for database lock.

# Ethical considerations

This study is conducted in accordance with the principles set forth in the ICH Harmonised Tripartite Guideline for Good Clinical Practice and the Declaration of Helsinki in its current version (see appendix), whichever affords the greater protection to the participants. The study will be reviewed by the Scientific Coodinating Committee of MRC Unit The Gambia at The London School of Hygiene and Tropical Medicine, the joint Gambian Government/MRC Unit The Gambia at the The London School of Hygiene and Tropical Medicine Ethics Committee and the Ethics Committee at Kings College London.

## General considerations on human subject protection

### Rationale for participant selection

Undernutrition during the early years of life has a harmful and irreversible impact on child growth and cognitive development. Many of the interventions tested to improve outcomes across infancy have had disappointing or inconsistent impact, a common feature being the absence of any attempts to provide nutritional supplements to infants during the first six months. With increasing evidence of micronutrient deficiencies in this age group, alongside strong evidence that growth and developmental deficits begin before six months, a renewed focus on the micronutrient status of infants is required.

This randomised, placebo-controlled efficacy trial of micronutrient supplementation to mothers (during pregnancy or pregnancy and lactation) and infants (Day 8 to six month of age) will be conducted among a population of women and their infants in a rural region of The Gambia, an area known to have high rates of micronutrient deficiencies. Conducting this trial among this population will identify the most efficacious way of improving micronutrient status in infancy, providing an evidence base for future effectiveness trials and policy recommendations relevant for both the Gambian context and other populations at high risk of micronutrient deficiencies.

### Evaluation of risks and benefits

Risks and benefits are considered separately for women and infants.

**Women (pregnancy)**: During pregnancy, all women will receive a (daily) multiple micronutrient supplement. The multiple micronutrient we propose to use is the UNIMMAP formulation, a preparation of 15 micronutrients specifically designed for pregnancy, and as formulated by UNICEF/WHO/UNU.[33] A single capsule provides the Recommended Dietary Allowance for each micronutrient (Appendix I). The UNIMMAP formulation has been used in multiple clinical trials globally and has been shown to offer similar benefits to women with respect to prevention of iron-deficiency anaemia and has been shown to outperform iron-folic acid with respect to several birth outcomes.[37] The most recent update to the WHO recommendations on antenatal care for a positive pregnancy experience includes the recommendation that antenatal multiple micronutrient supplements that include iron and folic acid are recommended in the context of rigorous research, where research in this context includes controlled clinical trials.[38] In line with WHO recommendations we do not, therefore, consider any risks associated with the pregnancy phase of this study but see benefit in providing all women enrolled into the study with multiple micronutrients, instead of iron folic acid, in view of the added benefit this formulation has been shown to confer to women and their infants.

**Women (post-partum)**: From delivery until six-months post-partum women will receive the same UNIMMAP preparation as used in the pregnancy phase (test) or a control preparation (maltodextrin) according to their initial trial arm allocation. Current policy does not include provision of iron folic acid or multiple micronutrients through the period of lactation. However, given the additional nutritional demands that lactation puts on a woman, we will test whether extending the supplementation period through the period of lactation confers additional health benefits to both mother and infant. A number of recent trials have included the UNIMMAP formulation in lactating women, with no adverse effects identified.[39] We do not therefore, identify any risks of the proposed intervention during lactation.

**Infancy**: From Day 8 to six-months of infant age, infants will receive a daily micronutrient supplement in the form of an infant syrup. To enable direct comparison between route of supplementation (trial Arms 1-4), the micronutrient formulation will be a combination of the same 15 micronutrients given to women during pregnancy and lactation, but at levels appropriate for this age group[40] (Appendix I). Arms 3 and 4 of the trial will receive a ‘basic’ supplement; Arm 5 will receive a formulation identical in composition to the basic infant micronutrient formulation, but with twice the dose and with the addition of choline (a nutrient essential for infant brain development known to be insufficient in this population[41]). Inclusion of this fifth ‘neuro-nutrient’ comparative arm will test the third research hypothesis, i.e. that a tailored neuro-nutrient MMN supplement targeted to infants will out-perform the standard formulation of micronutrients with respect to infant brain development. The formulation of the supplement is guided by the reported nutrient requirements of early brain development[15] and has been developed in accordance with dietary reference values for young infants.[40, 42]

Micronutrient syrups (single micronutrients, e.g. iron, vitamin D, or multiple micronutrients) are routinely given to clinically vulnerable groups, e.g. preterm infants, in many contexts.[43] Further, the level of micronutrients contained in the test products is parallel to the level included in many commercially available formula milks, and commonly given alongside breast milk in populations globally.[42] Identified benefits for infants receiving the test (micronutrient) formulation therefore includes the provision of additional micronutrients during a period of rapid growth and development and at a time where we hypothesise that many will be vulnerable to micronutrient deficiencies. It is possible that some infants may find the syrups difficult to tolerate, with side effects including vomiting and gastrointestinal discomfort. However, in the absence of comparable data we are unable to formally evaluate this risk, but would consider it low in view of the widespread used of micronutrient syrups in young infants globally.

## Informed consent

Individual consent for the study will be sought, with pregnant women providing consent for both herself and her infant. Field assistants will be trained to explain the full details of the project to all eligible women, covering all aspects of the study as laid out in the ‘Participant Information Sheet’. Literate parents will then be given the Information Sheet and study staff will be trained in accordance to the GG/MRC Joint Ethics Committee consent waiver in the applicable local languages for consenting of illiterate parents and will explain study information sheet to them in full in the language they understand. Illiterate consenting subjects will require an impartial literate witness to be present throughout the conseting procedure. Any questions that arise will be answered by the field assistants and one of the study investigators will also be available for further clarifications and explanations if required. Participation is entirely voluntary, and where women are willing to be involved, written Informed Consent will be obtained.

## Participant confidentiality

Any participants’ identifiable data collected by the study will be stored securely and their confidentiality protected in accordance with the Data Protection Act. Participant confidentiality, privacy and anonymity will always be ensured. All data will be anonymised and individuals will not be identifiable. The study will be run in compliance with the [MRC Corporate Information security Policy](http://www.mrc.ac.uk/documents/pdf/mrc-information-security-policy/) and the MRC Unit The Gambia’s Information and Communication Technology Security [POL-INT-001](http://mrcportal/Departments/InformationTechnology/Controlled%20documents/Policies%20(POL)/POL-INT-001_Information%20Technology%20and%20Security%20Policy/POL-INT-001_Information%20Security%20Policy_intranet.doc) available on the MRC Gambia intranet (available on request).

The risk to confidentiality is the personal information on subjects kept by the PI for study follow up verification purposes. These will be kept separate from the study data and not available to the study staff so that no linkages of personal data to study records would be easily made. The study data are stored in a limited access, password protected database so that only staff who have the required permissions can view the study records. Personal information will not be available to and study staff except the PI and the study’s Data Manager.

Subject to the required regulatory approvals, data about the participants may be shared in the future via a public data repository or by sharing directly with other researchers. In such cases, data will be fully anonymized and participant information will not be identifiable.

## Future use of stored specimen

Aliquots of blood, breast milk and urine from participating women and blood and stool samples from infants will be kept frozen at -70oC for future analysis. This may include DNA analysis and export of samples. We will obtain informed consent from the parents/guardians for this to be the case as part of the process of informed consent. The samples collected during the trial may be used to support other research in the future, and may be shared anonymously with other researchers, subject to the required approvals (including approval from the study PI and the joint Gambian Government/MRC Unit The Gambia at the the London School of Hygiene and Tropical Medicine Ethics Committee).

# Financing and insurance

King’s College London holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

Funding for the trial has been received from the Wellcome Trust (grant reference 220225/Z/20/Z).

# Publication policy

All key findings from this study will be disseminated via standard routes, including peer-reviewed journals and at international conferences. In addition, findings and the broader implications of the findings will be discussed with relevant stakeholders, both nationally in The Gambia (such as the National Nutrition Agency) and internationally (such as WHO). As this is a single site trial being conducted as part of a Fellowship award to the study PI, the PI will take responsibility for all publications resulting from the trial and publish according to the requirements of the funder (Wellcome Trust).

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Supplements, appendices and other documents

**Appendix I – Supplement Composition**

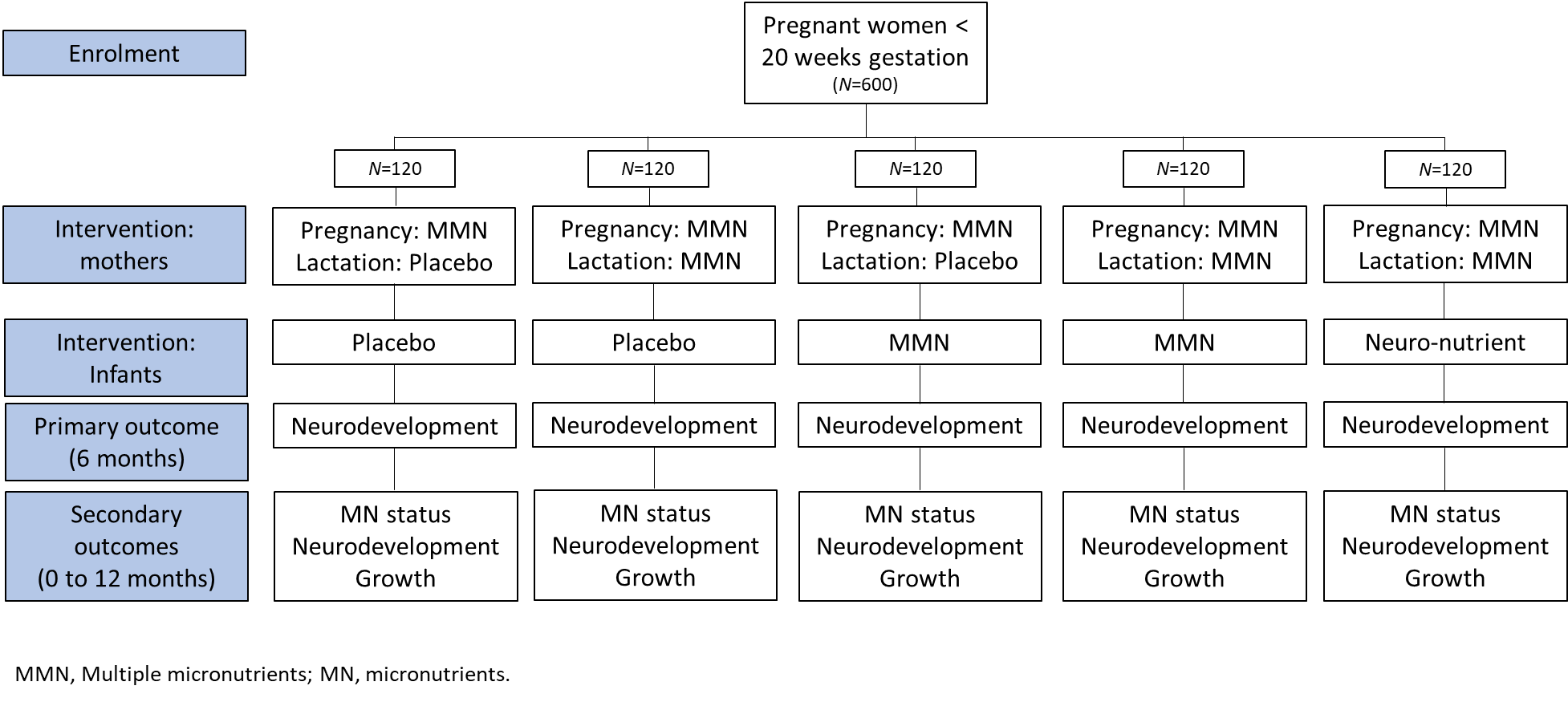
|  |  |  |  |
| --- | --- | --- | --- |
| **Micronutrients** | **Dose/day** | | |
|  | **UNIMMAP** | **Infant MMN** | **Infant neuro-nutrient** |
| Vitamin A (ug RE) | 800 | 350 | 700 |
| Vitamin D (IU) | 200 | 200 | 400 |
| Vitamin E (mg) | 10 | 2 | 4 |
| Thiamine (mg) | 1.4 | 0.2 | 0.4 |
| Riboflavin (mg) | 1.4 | 0.25 | 0.5 |
| Niacin (mg) | 18 | 3 | 6 |
| Folic acid (µg) | 400 | 50 | 100 |
| Vitamin B6 (mg) | 1.9 | 0.25 | 0.5 |
| Vitamin B12 (µg) | 2.6 | 0.4 | 0.8 |
| Vitamin C (mg) | 70 | 12 | 24 |
| Zinc (mg) | 15 | 1.5 | 3 |
| Iron (mg) | 30 | 2.2 | 4.4 |
| Iodine (µg) | 150 | 45 | 90 |
| Selenium (µg) | 65 | 10 | 20 |
| Copper (mg) | 2 | 0.3 | 0.6 |
| Choline (mg) |  |  | 125 |

For the MMN intervention arms during pregnancy and lactation, we will use the UNIMMAP formulation.[33]

For infants in the MMN intervention arm, we will use the same 15 micronutrients as in UNIMMAP, but at levels appropriate for this age group.[42]

For the neuro-nutrient arm, we will use the same preparation as the infant MMN arms, but at twice the dose and with the addition of choline (a nutrient essential for infant brain development known to be insufficient in this population).[41] These levels are below the maximum level for young infants, according to both EFSA [40]and the Codex Alimentarius of the FAO.[42]

**Schematic of Study Design**:



Appendix: Schedule of events



**Appendix:**

**World Medical Association Declaration of Helsinki**

**Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964  
and amended by the:  
29th WMA General Assembly, Tokyo, Japan, October 1975  
35th WMA General Assembly, Venice, Italy, October 1983  
41st WMA General Assembly, Hong Kong, September 1989  
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996  
52nd WMA General Assembly, Edinburgh, Scotland, October 2000   
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)  
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)  
59th WMA General Assembly, Seoul, Republic of Korea, October 2008  
64th WMA General Assembly, Fortaleza, Brazil, October 2013

**Preamble**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

**General Principles**

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study’s findings and conclusions.

**Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

**Informed Consent**

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject’s dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

1. Brain Imaging for Global Health (BRIGHT); an ongoing longitudinal study of neurocognitive development using brain imaging in rural Gambian and UK (Cambridge) infants. [↑](#footnote-ref-1)