

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

|  |   |   |
|--|---|---|
| <b>Submission date</b><br>01/07/2021   | <b>Recruitment status</b><br>Recruiting | <input checked="" type="checkbox"/> Prospectively registered<br><input checked="" type="checkbox"/> Protocol            |
| <b>Registration date</b><br>09/07/2021 | <b>Overall study status</b><br>Ongoing  | <input checked="" type="checkbox"/> Statistical analysis plan<br><input type="checkbox"/> Results                       |
| <b>Last Edited</b><br>13/09/2024       | <b>Condition category</b><br>Other      | <input type="checkbox"/> Individual participant data<br><input checked="" type="checkbox"/> Record updated in last year |

## Plain English summary of protocol

### Background and study aims

Undernutrition (a deficiency of calories or of one or more essential nutrients) 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 a disappointing or inconsistent impact, a common feature being the absence of any attempts to provide nutritional supplements to infants during the first 6 months. With increasing evidence of micronutrient (vitamin/mineral) deficiencies in this age group, alongside strong evidence that growth and developmental deficits begin before 6 months, a renewed focus on the micronutrient status of infants is required.

This is a study of micronutrient supplementation given to mothers (during pregnancy or pregnancy and lactation) and infants (birth to age 6 months) in rural Gambia, where rates of micronutrient deficiencies are high. This study will identify the most effective way of improving micronutrient status in infancy, and assess the impact on infant developmental outcomes, providing evidence for future trials and policy recommendations.

### Who can participate?

Pregnant women (less than 20 weeks of gestation at their enrolment visit, with a single pregnancy), aged 18 to 49 years of age and living in the West and Central Kiang regions of The Gambia

### What does the study involve?

During pregnancy, all women will receive a (daily) multiple micronutrient supplement. The multiple supplement is the UNIMMAP formulation, a preparation of 15 micronutrients specifically designed for pregnancy, and as formulated by UNICEF/WHO/UNU. A single tablet provides the Recommended Dietary Allowance for each micronutrient.

From delivery until 6 months later women will be randomly allocated to receive the same UNIMMAP preparation as used in the pregnancy phase (test) or a control preparation (maltodextrin).

From day 8 to 6 months of age, infants will receive a daily micronutrient supplement in the form of an infant syrup. To enable direct comparison between routes of supplementation, 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. Two groups will receive a 'basic' supplement; another group 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).

What are the possible benefits and risks of participating?

The UNIMMAP formulation has been used in multiple clinical trials globally and has been shown to offer similar benefits to women with respect to the prevention of iron-deficiency anaemia and has been shown to outperform iron-folic acid with respect to several birth outcomes. 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. In line with WHO policy the researchers do not therefore consider there to be any risks associated with the pregnancy phase of this study but see a benefit in providing all women enrolled on 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.

Current policy does not include the 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, the researchers will test that extending the supplementation period through the period of lactation confers additional health benefits to both mother and infant. A number of recent studies have included the UNIMMAP formulation in lactating women, with no adverse effects identified. The researchers do not therefore expect any risks of the proposed intervention during lactation.

The study will test whether 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 and has been developed in accordance with dietary reference values for young infants.

Micronutrient syrups (single micronutrients, e.g. iron, vitamin D, or multiple micronutrients) are routinely given to clinically vulnerable groups, such as preterm infants, in many contexts. 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. Identified benefits for infants receiving the test (micronutrient) formulation therefore include the provision of additional micronutrients during a period of rapid growth and development and at a time where 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 the researchers are unable to formally evaluate this risk, but would consider it low in view of the widespread use of micronutrient syrups in young infants globally.

Where is the study run from?

King's College London (UK) and the MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine (Gambia)

When is the study starting and how long is it expected to run for?

September 2020 to August 2027

Who is funding the study?

The Wellcome Trust (UK)

Who is the main contact?

Dr Sophie Moore

sophie.moore@kcl.ac.uk

## Contact information

### Type(s)

Scientific

### Contact name

Dr Sophie Moore

### ORCID ID

<http://orcid.org/0000-0003-1650-3238>

### Contact details

10th Floor North Tower

St Thomas' Hospital

Westminster Bridge Road

London

United Kingdom

SE1 7EH

+44 (0)20 7188 3639

sophie.moore@kcl.ac.uk

## Additional identifiers

### EudraCT/CTIS number

Nil known

### IRAS number

### ClinicalTrials.gov number

Nil known

### Secondary identifying numbers

1.1

## Study information

### Scientific Title

Improving Infant Neurocognitive Development and Growth Outcomes with Micronutrients (INDiGO)

### Acronym

INDiGO

### Study objectives

1. Maternal supplementation with multiple micronutrients (MMN) across pregnancy and lactation confers a greater benefit to infant brain development than supplementation in pregnancy alone.
2. Direct supplementation of MMN to infants from birth to 6 months of age, alongside breastfeeding, confers a 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.

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

Approved 12/05/2021, The Gambia Government / MRC Joint Ethics Committee (c/o MRC Unit The Gambia@LSHTM, Fajara, PO Box 273, Banjul, The Gambia, West Africa; + 220 (0)4495442-6 Ext. 2308; ethics@mrc.gm), ref: 25071

## **Study design**

Single-centre interventional double-blind randomized controlled efficacy trial

## **Primary study design**

Interventional

## **Secondary study design**

Randomised controlled trial

## **Study setting(s)**

Community

## **Study type(s)**

Other

## **Participant information sheet**

See additional files

## **Health condition(s) or problem(s) studied**

Infant neurocognitive development and growth

## **Interventions**

During pregnancy and lactation women will be randomised to receive a daily multiple micronutrient (MMN) supplement (capsule) or placebo. For the MMN intervention arms, the researchers will use the UNIMMAP formulation, a preparation of 15 micronutrients specifically designed for pregnancy, and as formulated by UNICEF/WHO/UNU. A single capsule provides the Recommended Dietary Allowance for each micronutrient. Placebo capsules (maltodextrin) will look and taste identical.

All women will receive the UNIMMAP supplement during pregnancy and randomisation to the intervention (UNIMMAP) or placebo capsule will start post-delivery. From delivery until 6 months post-partum women will be randomized to receive the same UNIMMAP preparation as used in the pregnancy phase (test) or a control preparation (maltodextrin).

From birth until 6 months of age, infants will receive a daily supplement of MMNs or placebo. To enable direct comparison between routes of supplementation (trial arms 1-4), the MMN 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). 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 MMN formulation, but with twice the dose and with the addition of choline. Inclusion of this fifth 'neuro-nutrient' (NN) 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 MMN with respect to infant brain development.

The infant interventions/placebo will be provided as a syrup and dropped directly into the infant's mouth. Supplementation will commence in the second week of life, after the infant has been named (Day 7 in The Gambia; prior to this the mother-infant pair have a period of confinement for breastfeeding to establish).

## **Intervention Type**

Supplement

## **Primary outcome measure**

Infant neurodevelopment assessed using functional near-infrared spectroscopy (fNIRS) when infants are 6 months of age

## **Secondary outcome measures**

1. Infant micronutrient status (iron, iodine, choline, vitamin B12) measured by blood/urine analysis on samples collected at 1, 6 and 12 months of infant age
2. Growth measured by assessment of infant size (weight, length, mid-upper arm circumference, head circumference) at monthly visits from birth until 12 months of infant age
3. Neurocognitive development measured by a behavioural assessment (Mullen Scales of Early Learning) and measures of brain function using functional near-infrared spectroscopy (fNIRS) and eye-tracking technology at 1, 6 and 12 months of infant age

## **Overall study start date**

01/09/2020

## **Completion date**

31/08/2027

# **Eligibility**

## **Key inclusion criteria**

1. Pregnant women aged 18-49 years
2. Singleton pregnancy at <20 weeks gestation at initial pregnancy confirmation
3. Healthy, with no evidence of current severe anaemia (haemoglobin >7 g/dl)
4. Willingness to take a daily trial product (capsule) daily from 20 weeks of pregnancy until 6 months post-partum and for their infant to receive a daily trial product (syrup drops) from Day 8 until 6 months of age

## **Participant type(s)**

Healthy volunteer

**Age group**

Mixed

**Lower age limit**

18 Years

**Upper age limit**

49 Years

**Sex**

Both

**Target number of participants**

600 mother-infant pairs

**Key exclusion criteria**

Pregnancy:

1. Multiple pregnancy
2. Pregnancy  $\geq 20$  weeks gestation
3. Severe anaemia (haemoglobin  $< 7$  g/dl)
4. Any history or evidence of chronic disease (including HIV, TB, hypertension)
5. Unwilling to avoid the ingestion of other micronutrient supplements during the study period

Post-partum/infancy:

1. Very or extremely preterm infants ( $< 32$  weeks gestation at delivery)
2. Very low birth weight infants ( $< 1.5$  kg at delivery)
3. Infants identified at any follow-up point as having severe-acute malnutrition (weight-for-height z score of  $< -3SD$ )
4. Non-breastfeeding mother-infant pairs
5. Unwilling to avoid the ingestion of – or for their infant to avoid the ingestion of – other micronutrient supplements during the study period
6. 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)

**Date of first enrolment**

01/04/2023

**Date of final enrolment**

31/12/2025

**Locations****Countries of recruitment**

Gambia

**Study participating centre**

**MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine**

Fajara

PO Box 273

Banjul

Gambia

-

## **Sponsor information**

### **Organisation**

King's College London

### **Sponsor details**

c/o Amy Holton

Quality Manager

King's Health Partners Clinical Trials Office

5.35 James Clerk Maxwell Building

57 Waterloo Road

London

England

United Kingdom

SE1 8WA

+44 (0)7703469925

amy.holton@kcl.ac.uk

### **Sponsor type**

University/education

### **Website**

<http://www.kcl.ac.uk/index.aspx>

### **ROR**

<https://ror.org/0220mzb33>

## **Funder(s)**

### **Funder type**

Research organisation

### **Funder Name**

Wellcome Trust

### **Alternative Name(s)**

Wellcome, WT

## Funding Body Type

Private sector organisation

## Funding Body Subtype

Trusts, charities, foundations (both public and private)

## Location

United Kingdom

# Results and Publications

## Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal. The study protocol and statistical analysis plan are not yet available.

## Intention to publish date

01/12/2027

## Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from the principal investigator Dr Sophie Moore (sophie.moore@kcl.ac.uk). Investigators wishing to access data and/or samples will additionally require approval from the MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine (MRCG@LSHTM) Scientific Coordinating Committee and the joint Gambian Government/MRCG@LSHTM Ethics Committee (<https://www.mrc.gm/scientific-coordinating-committee/>). No additional consent from study participants will be required. Full access to data and samples will be possible 12 months following the collection of the final data point. Only fully anonymized data will be available, with no capacity for linkage back to individual participant details. Working with the research governance offices at both KCL and MRCG@LSHTM, full GDPR compliance will be ensured.

## IPD sharing plan summary

Available on request

## Study outputs

| Output type                                   | Details      | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|--------------|--------------|------------|----------------|-----------------|
| <a href="#">Participant information sheet</a> | version V1.1 | 02/07/2021   | 09/07/2021 | No             | Yes             |
| <a href="#">Participant information sheet</a> | V3.0         | 20/12/2023   | 13/09/2024 | No             | Yes             |
| <a href="#">Protocol article</a>              |              | 16/07/2024   | 13/09/2024 | Yes            | No              |
| <a href="#">Statistical Analysis Plan</a>     | V1.0         | 28/03/2024   | 13/09/2024 | No             | No              |