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

Submission date 01/07/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [X] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 09/07/2021	**Overall study status** Ongoing	
Last Edited 15/10/2025	**Condition category** Other	

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
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
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)
1. Approved 12/05/2025, Joint Gambia Government / MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine Ethics Committee (c/o MRC Unit The Gambia, Fajara, PO Box 273, Gambia; + 220 4495442; ethics@mrc.gm), ref: 25071
2. Approved 14/12/2021, Research Ethics Committee, King's College London (Franklin Wilkin Building, London, SE1 9NH, United Kingdom; 02078484020; rec@kcl.ac.uk), ref: RESCM-21/22-23914

Primary study design
Interventional

Study design
Single-centre interventional double-blind randomized controlled efficacy trial

Study type(s)
Other

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

Key secondary outcome(s)
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

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

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
49 Years

Sex
All

Total final enrolment
617

Key exclusion criteria
Pregnancy:
1. Multiple pregnancy
2. Pregnancy ≥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
02/07/2025

Locations

Countries of recruitment
Gambia

Study participating centre
MRC Unit The Gambia at the London School of Hygiene and Tropical Medicine
Fajara
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Sponsor information

Organisation
King's College London

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

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?
Protocol article		16/07/2024	13/09/2024	Yes	No
Participant information sheet	version V1.1 V3.0	02/07/2021	09/07/2021	No	Yes

Participant information sheet	V1.0	20/12/2023	13/09/2024	No	Yes
Statistical Analysis Plan		28/03/2024	13/09/2024	No	No