International Centre for Diarrhoeal Disease Research, Bangladesh
CENTRE FOR HEALTH & POPULATION RESEARCH
Mail : ICDDR,B, GPO Box 128, Dhaka-1000, Bangladesh
Phone: 880-2-8811751-60, Fax : 880-2-8823116, 8812530
Web : http://www.icddrb.org

PHSD 2002

Memorandum

23 May 2006

To : Dr. Shams El Arifeen
Principal Investigator of research protocol # 2002-031
Public Health Sciences Division (PHSD)

From: Chairman
Research Review Committee (RRC)

Sub : **Approval of the proposal for an addendum to research protocol # 2002-031**

Thank you for your memo dated 17 May 2006 and the modified version of the proposal for an addendum to your research protocol # 2002-031 titled "Combined interventions to promote maternal and infant health: Effects over a pregnancy cycle and on children 0-24 months". Upon satisfactory addressing of the issues raised by the Committee on your proposal in its meeting held on May 4, 2006, approval of the proposal for an addendum to your above-mentioned research protocol is hereby accorded.

Other terms and conditions for implementation of your research protocol as contained in my memo dated 22 November 2002 according initial approval of the research protocol shall, however, remain unchanged.

Thank you once again.

Copy: Director, PHSD

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Cable : Cholera Dhaka

To: Chairperson, RRC
ICDDR,B

17 May 2006

Through: For Director, PHSD 21/5/06

From: Dr Shams El Arifeen
PI: Research Protocol #2002-031 and
Head, Child Health Unit, PHSD

Subject: Research Protocol # 2002-031 "Combined interventions to promote maternal and infant health: Effects over a pregnancy cycle and on children 0-24 months"

Thank you for your review of the Addendum of the above protocol and for your comments. Responses to specific comments are given below:

1. Though the addendum proposal is based upon preliminary findings, providing those findings would enable to assess the strength of association.

   -As advised, we have now provided the preliminary findings in a table in the Addendum(Pg 18a).

2. Expressions of which cytokines would be sought from the placental tissues ?

   - In the 1st (index) pregnancy, we have looked at both pro-inflammatory as well as TH1 and TH2 types of cytokines. It appears that only pro-inflammatory and Th1 type of cytokines are detectable in placental tissue by immunostaining. Therefore, we would continue to study the same cytokines in the next pregnancy, namely TNF-α, IL-1β (pro-inflammatory) and IFN-γ (TH1)(Pg 18a).

3. Budgetary provisions have not been attached to the addendum proposal, though additional costs would be involved.

   -Budget has now been provided.

4. Bangla version of the consent form should be submitted for review by the committee.

   -Bangla version of the consent form has been included.

We have added the necessary changes as advised by the committee and hope that the protocol after the suggested modifications is acceptable in its present form.

Thank you.

REQUEST FOR ADDENDUM TO/MODIFICATION OFAPPROVED RESEARCH PROTOCOL

PART- I: Research Protocol Information

Research protocol number: 2002-031

Title: Combined Interventions to Promote Maternal and Infant Health: Effects Over a Pregnancy Cycle and on Children 0-24 Months

Principal Investigator: Dr. Shams El Arifeen Division: Public Health Sciences Division

Date of approval: RRC 03-11-2002 ERC 20-11-2002 AEEC X

Have the protocol activities been started? ☐ No ☒ Yes Date of starting:

If yes, current status of implementation of the research protocol
(check all boxes that are applicable):

☐ Continuing enrolment of the study participants
☒ Enrollment closed but follow-up or data analysis are continuing
☒ Continuing laboratory assays
☒ Writing manuscript
☐ Protocol activities are closed and completion report submitted
☐ Others, please specify:

Indicate if this is the first proposal for change(s)/modification(s)/addendum to the research protocol?

☐ Yes ☒ No

If No, Part II of the form be completed

PART- II:
Particulars of previously approved addendum to/modification of the research Protocol

Number	Description of approved addendum to/Modification of the research protocol	Approval date		
		RRC	ERC	AEEC
1	Salivary cortisol and maternal-infant interaction	19-02-03	19-05-03	X
2	Salivary cortisol and maternal-infant interaction	23-12-03	05-01-04	X
3	Follow-up of mothers into next pregnancy and child birth	18-04-04	03-06-04	X

PART –III: Particulars of proposed addendum to/modification
Proposed changes affects: (check all that are applicable)

☐ Principal or other investigators.
☐ Study objective(s).

☒ Research procedure(s).
☐ Number of participants to be studied.
☐ Age and/or sex group of the study participants or addition of special group(s)e.g. pregnant women, malnourished children.
☐ Eligibility (inclusion and exclusion) criteria.
☐ Intervention (drug/vaccine formulation or dosing) or devise.
☒ Collection of biological samples (type, number of tests, amount of sample).
☐ Consent process.
☐ Consent forms.
☐ Study instrument (questionnaire, FGD guidelines etc.).
☐ Study sites.
☐ Compensation for participation in research (e.g. increasing/decreasing the amount).
☒ Data Collection/analysis.
☐ Budget.
☐ Others, please specify:

A. Provide itemized description of the proposed changes and their rationale/justifications.

1. An aim of the on-going study (Protocol # 2002-031) is to evaluate the effect of food and micronutrient supplementation of pregnant women on immune functions at birth (cord blood, placenta) and in infants at 6 and 12 months of age. Preliminary findings show a potential effect of the interventions on newborn immune functions (below). The approved protocol includes follow-up of the study women through their next pregnancies and assessment of maternal anthropometry in the next pregnancy, collection of blood samples, and birth weight and breastfeeding of the 2nd child.

2. The study provides a unique opportunity to assess if the immune function effects in the first child carry over into the next child.

3. We propose to collect placental tissue and cord blood samples (20 ml) the study women during the delivery of their next babies. We note that the collection of these specimens do not involve invasive procedures.

4. The cord blood samples will be analyzed for lymphocyte proliferation response and their populations and sub-populations by three colour fluorescence analysis using a FACSort flow cytometer as well as leptin levels in the plasma. The placental specimens will be analyzed for expression and localization pattern of T lymphocytes, granulocytes and cyokines (TNF-α, IL-1β (pro-inflammatory) and IFN-γ (TH1)

B. Please respond to the followings:

a) Is the request based on any new finding(s)?

☒ Yes ☐ No

If yes, describe the significance of the finding(s) (e.g. new adverse event) available during the course of research, or information concerning requested change(s) that may influence study participants' willingness to continue participation. In such events, the PI shall modify the consent form(s) and apply that for re-consenting of participants already enrolled in the study.

Preliminary data from the 1st (index) pregnancy of the enrolled women indicates that supplementation with 60 mg Fe leads to a significant increase in cord blood leptin levels that was positively associated with birth weight. Significantly increased numbers of macrophages and a marked reduction in pro-inflammatory cytokine expression in the placental tissue indicated increased immune surveillance and reduced inflammatory responses. The approved protocol involves follow-up of the women

through their next pregnancies and thus provides an opportunity to assess if these effects persist across pregnancies.

Table. Semiquantitative expression of immunostaining in placental tissue from women supplemented with various micronutrient formulations.

Study Groups	30 mg Fe + folic acid	60 mg Fe + folic acid	P value	MUM + 30 mg Fe + folic acid	P value
	Placental tissue				
CD3	15.5 ± 4.3	10 ± 2.2	0.64	9.46 ± 2.1	0.84
CD8	8 ± 3.4	4 ± 1.1	0.24	3.7 ± 0.9	0.8
Macrophages	4.9 ± 1.5	9.4 ± 2	0.08	3.3 ± 1	0.03*
Neutrophils (MPO)	16.4 ± 2.2	18.4 ± 2.4	0.4	17.2 ± 2	0.7
TNF-α	0.56 ± 0.29	0.64 ± 0.32	0.62	1.24 ± 0.54	0.8
IFNγ	0.96 ± 0.29	0.86 ± 0.3	0.47	0.54 ± 0.24	0.44
IL-1β	0.4 ± 0.11	0.11 ± 0.02	0.02*	0.44 ± 0.16	0.1
	Cord blood plasma				
Leptin, ng/ml	3.35 ± 0.35	4 ± 0.35	0.06	3.3 ± 0.30	0.01

b) Will the requested change(s) alter/likely to alter the scientific validity of the study?

☐ Yes ☒ No

If yes, please explain that in detail

c) Do any of the proposed change(s)/amendment(s) alter the risk (physical, psychological and sociological) /or benefit to the study participants?

☐ Yes ☒ No

If yes, explain in detail:

d) If answer to the question # (c) is 'YES', will the enrolled participants be willing to remain in the study; and/or currently enrolled study participants need to be informed or re-consented.

☐ Yes ☐ No

If yes, describe, how will this be done?

e) Do the proposed change(s)/modification(s)/addendum affect any other services benefits?

☐ Yes ☒ No

If, yes, explain in detail:

f) Any other relevant information, which might not have covered above:

I understand that I cannot initiate any change in the approved research protocol until my requested change(s) is/are approved by all relevant Committees/bodies.

Date:

Signature of the Principal Investigator

Endorsed

Division Director

Date 21 May, 2006

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Memorandum

7 May 2006

To : Dr. Shams El Arifeen
Principal Investigator of research protocol # 2002-031
Public Health Sciences Division (PHSD)

From: Prof. Alejandro Cravioto
Chairman
Research Review Committee (RRC)

Sub : Proposal for modification of research protocol # 2002-031

Thank you submitting the proposal for modifications of your research protocol # 2002-031 titled "Combined interventions to promote maternal and infant health: Effects over a pregnancy cycle and on children 0-24 months" for consideration of the RRC and presenting the proposal before the RRC in its meeting held on May 4, 2006. This is to inform you that after review and discussion, the Committee made following observations on the proposal:

a) Though the addendum proposal is based upon preliminary findings, providing those findings would enable to assess the strength of association.

b) Expressions of which cytokines would be sought from the placental tissues?

c) Budgetary provisions have not been attached to the addendum proposal, though additional costs would be involved.

d) Bangla version of the consent form should be submitted for review by the Committee.

You are advised to modify the proposal addressing above issues and to submit its modified version for consideration of the RRC Chair.

Thank you once again.

Copy: Director, PHSD

CHU

ICDDR,B Centre for Health & Population Research — RRC APPLICATION FORM

RESEARCH PROTOCOL

Protocol No. 2002-031

FOR OFFICE USE ONLY	
RRC Approval:	☐ Yes / ☐ No Date:
ERC Approval:	☐ Yes / ☐ No Date:
AEEC Approval:	☐ Yes / ☐ No Date:

Project Title: Combined Interventions to Promote Maternal and Infant Health: Effects Over a Pregnancy Cycle and on Children 0-24 Months

Theme: *(Check all that apply)*

- ☒ Nutrition
- ☐ Emerging and Re-emerging Infectious Diseases
- ☐ Population Dynamics
- ☒ Reproductive Health
- ☐ Vaccine evaluation
- ☐ HIV/AIDS
- ☐ Environmental Health
- ☐ Health Services
- ☒ Child Health
- ☐ Clinical Case Management
- ☒ Social and Behavioural Sciences

Key words: Food supplementation, iron supplementation, micronutrient supplementation, pregnancy, foetal growth restriction, birth weight, infant growth, morbidity, immune function, motor milestones, cognitive development, maternal depletion

Relevance of the protocol: This protocol is a follow-up to the protocol **Combined Interventions to Promote Maternal and Infant Health (2000-025)**. The first protocol addresses *four combined interventions in a cohort of pregnant women,* aiming at detailed knowledge about different combinations of interventions and their effects on primarily birth weight and maternal haemoglobin. Interventions are randomised regarding early and later start of food supplementation, type of micronutrient supplementation, treatment for asymptomatic bacterial vaginosis, and counselling for exclusive breast-feeding. This second protocol deals with the potential positive health effects assessed over the entire pregnancy cycle of the mother, and during 2 years of follow-up of the child: (1) the effects on maternal nutrition during the whole pregnancy cycle and on the birth weight of the subsequent child; (2) effects on lactation and exclusive breast feeding; (3) effects on infant growth and micronutrient status; (4) effects on infant motor and cognitive development; and (5) effects on development of immune function and morbidity of the infant. An evaluation of these functional outcomes is needed for a comprehensive assessment of benefit of the interventions and cost benefit analyses.

Principal Investigator: Lars Ake Persson **Division: PHSD** **Phone:** 9885155

Address: ICDDR,B **Email: persson@icddrb.org**

Co-Principal Investigator(s): Shams Arifeen (co-ordinating), Dewan Alam (growth, morbidity), Rubhana Raqib (immune function), Jena D Hamadani (psycho-motor development)

Co-Investigator(s): ICDDR,B: Alam, Dewan; Blum, Lauren; Chakraborty, J; Dhar Badal; Ekstrom, Lotta; Hoque, Waheedul; Kabir, I; Naved, Ruchira; Rahman, Anisur; Rahman, Montiur; Saha, Kuntal; Shahen, Rubina; Shahid, Nigar; Streatfield, Peter Kim; Tofail, Fahmida; Wagatsuma, Yukiko; Wahed, MA; Yunus, Md. BRAC: Chowdhury, Mushtaq; Mahmud, Zeba.
Cornell university: Rasmussen, Kathleen; Frongillo, Ed; Pelto, Gretel; Habicht, J-P; Haas, Jere LSH&TM: Collison, Andrew; Moore, Sophie; Prentice, Andrew. Institute of Child Health, London: Grantham McGregor, Sally. Umeå University: Lindholm, Lars; UC Davis: Lönnerdal, Bo; Royal London Hospital: Graham Hitman

Collaborating Institute(s): BRAC; Cornell University; London School of Hygiene & Tropical Medicine; Institute of Child Health, London; Umeå University; UC Davis; London University

Population: Inclusion of special groups *(Check all that apply)*:

Gender
- ☒ Male
- ☒ Pregnant Women
- ☒ Fetuses

☒ Females

Age

☒ 0 – 4 years

☐ 5 – 9 years

☒ 10 – 19 years

☒ 20 +

☐ > 65

☐ Prisoners

☐ Destitutes

☐ Service providers

☐ Cognitively Impaired

☐ CSW

☐ Others (specify _____)

☐ Animal

Revised on: 7 July 2002

Project / study Site *(Check all that apply)*:

☐ Dhaka Hospital

☐ Matlab Hospital

☒ Matlab HDSS area

☐ Matlab non-HDSS area

☐ Mirzapur

☐ Dhaka Community

☐ Chakaria

☐ Abhoynagar

☐ Mirsarai

☐ Patyia

☐ Other areas in Bangladesh

☐ Outside Bangladesh
name of country:

☐ Multi centre trial
(Name other countries involved)

_____

Type of Study *(Check all that apply)*:

☐ Case Control study

☒ Community based trial / intervention

☒ Program Project (Umbrella)

☐ Secondary Data Analysis

☐ Clinical Trial (Hospital/Clinic)

☐ Family follow-up study

☐ Cross sectional survey

☒ Longitudinal Study (cohort or follow-up)

☐ Record Review

☒ Prophylactic trial

☒ Surveillance / monitoring

☐ Others

Targeted Population *(Check all that apply)*:

☒ No ethnic selection (Bangladeshi)

☐ Bangalee

☐ Tribal groups

☐ Expatriates

☐ Immigrants

☐ Refugee

Consent Process *(Check all that apply)*:

☒ Written

☒ Oral

☐ None

☒ Bengali language

☒ English language

Total sample size: 3000

Determination of Risk: Does the Research Involve *(Check all that apply)*:

☐ Human exposure to radioactive agents?

☐ Fetal tissue or abortus?

☐ Investigational new device?
(specify _____)

☐ Existing data available from Co-investigator

☐ Human exposure to infectious agents?

☐ Investigational new drug

☐ Existing data available via public archives/source

☒ Pathological or diagnostic clinical specimen only

☐ Observation of public behaviour

☐ New treatment regime

Yes/No

☐ ☒ Is the information recorded in such a manner that subjects can be identified from information provided directly or through identifiers linked to the subjects?

☐ ☒ Does the research deal with sensitive aspects of the subject's behaviour; sexual behaviour, alcohol use or illegal conduct such as drug use?

Could the information recorded about the individual if it became known outside of the research:

☐ ☒ a. place the subject at risk of criminal or civil liability?

☐ ☒ b. damage the subject's financial standing, reputation or employability; social rejection, lead to stigma, divorce etc.

Do you consider this research *(Check one)*:

☐ greater than minimal risk
☒ no more than minimal risk
☐ no risk
☐ only part of the diagnostic test

Minimal Risk is "a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as a part of routine physical examination".

Yes/No

☒ ☐ Is the proposal funded?

If yes, sponsor Name: UNICEF, DfID

Yes/No

☒ ☐ Is the proposal being submitted for funding?

If yes, name of funding agency: (1) UNICEF

(2) _____

Do any of the participating investigators and/or their immediate families have an equity relationship (e.g. stockholder) with the sponsor of the project or manufacturer and/or owner of the test product or device to be studied or serve as a consultant to any of the above?

IF YES, submit a written statement of disclosure to the Director.

Dates of Proposed Period of Support *(Day, Month, Year - DD/MM/YY)*	**Cost Required for the Budget Period ($)**
Beginning date Oct 2002	*a. Ist Year* _____ *2nd Year* _____ *3rd Year* _____ *Other years* _____
End date Dec 2006	*b. Direct Cost*: _____ *Total Cost*: 1605,000 $

Approval of the Project by the Associate Director of the Applicant

The above-mentioned project has been discussed and reviewed at the Division level as well by the external reviewers. The protocol has been revised according to the reviewer's comments and is approved.

Lars Åke Persson		4 Oct 2002
Name of the Associate Director	Signature	Date of Approval

Certification by the Principal Investigator

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

Signature of PI

Date: 5 Oct 2002

Name of Contact Person (if applicable)

Table of Contents

[x] Check here if appendix is included

PROJECT SUMMARY: Describe in concise terms, the hypothesis, objectives, and the relevant background of the project. Describe concisely the experimental design and research methods for achieving the objectives. This description will serve as a succinct and precise and accurate description of the proposed research is required. This summary must be understandable and interpretable when removed from the main application. (TYPE TEXT WITHIN THE SPACE PROVIDED).

Principal Investigator Lars Ake Persson

Project Name **Combined Interventions to Promote Maternal and Infant Health: Effects Over a Pregnancy Cycle and on Children 0-24 Months**

Total Budget	1605,000 $	Beginning Date	Oct 2002	Ending Date Dec 2006

This protocol describes the continuation of the previously approved protocol "Combined Interventions to Promote Maternal and Infant Health" (RRC 2000-025), that has received the acronym MINIMat, short for Maternal and Infant Nutrition Interventions in Matlab. It deals with the functional outcomes of four combined interventions over an entire pregnancy cycle and during a follow-up of the offspring from birth to two years. Though we know that maternal nutritional status is the main predictor of intrauterine growth in developing countries and that size at birth is an important determinant of infant growth and mortality, the results of nutritional supplementation trials with pregnant women in different parts of the world have been quite mixed. We are performing *interventions in a cohort of pregnant women*, aiming at detailed knowledge about different combinations of interventions. Four combined interventions are conducted in a group of about 3,000 undernourished women who live in Matlab upazila, Bangladesh - the well-established field site of ICDDR,B: Centre for Health and Population Research. An on-going demographic surveillance program identifies pregnant women within 6-8 wk of conception. (1) We are randomly assigning women to receive advice to begin the food supplementation program (a) immediately after identification of pregnancy (early care) or (b) at the time of their choosing (usual care). (2) Within each of these groups, we randomly assign women to receive a pill that contains (a) 30 mg Fe and 400 µg folic acid or (b) 60 mg Fe and 400 µg folic acid (usual care) or (c) 30 mg Fe, 400 µg folic acid and 13 additional micronutrients. (3) All women are offered screening for bacterial vaginosis (BV). Within each of the six groups mentioned above asymptomatic BV-positive women are randomly assigned to (a) 250 mg metronidazole orally thrice daily for 7 days or (b) lactose tablets given with the same dose frequency. (4) We randomly assign all of the subjects to receive either (a) counselling for exclusive breastfeeding (EBF) or (b) a different health education message of equivalent intensity. Each of these trials is designed to address an important scientific issue and also uses an intervention that could be readily incorporated into public health programs. The combinations of the interventions will allow for analysis of combined effects and interactions between the interventions. The effects evaluated in the main study focus on the nutritional effects in the pregnant woman and the effects on foetal growth and size at birth. The potential *long-term functional effects are in this follow-on protocol evaluated over the entire pregnancy cycle of the mother, and during a few years of follow-up of the child*: (A) Evaluating the effects on maternal nutrition during the whole pregnancy cycle, and on the birth weight of the subsequent child, (B) Evaluating the effects of breastfeeding counselling on lactation and exclusive breast feeding, (C) Assessing the effects on infant growth and micronutrient status, (D) Evaluating the effects on motor and cognitive development, and (E) Assessing the effect of the nutrition interventions on the development of the immune function and morbidity of the infant. An evaluation of these functional outcomes is needed for a comprehensive assessment of benefit of the interventions.

KEY PERSONNEL (List names of all investigators including PI and their respective specialties)

Name	Professional Discipline/ Speciality	Role in the Project
ICDDR,B:		
Lars Åke Persson	Epidemiologist, paediatrician	PI
Shams Arifeen	Child health epidemiologist	Co-PI
Dewan Alam	Nutrition epidemiologist	Co-PI (growth, morbidity)
Rubhana Raqib	Immunologist	Co-PI (Immune function)
Jena D Hamadani	SMO GrII/Paediatrics	Co-PI (p-m development)
Fahmida Tofail	MO Paediatrics	p-m development
Lauren Blum	Nutrition anthropologist	Ethnographic components
J Chakraborty	Senior manager	Field co-ordination
Badal Dhar	Programmer	Data base system
Lotta Ekström	Nutritionist, epidemiologist	Micronutrients
Waheedul Hoque	MO	Co-ordinator of study
Iqbal Kabir	MO, clinical scientist	EBF intervention
Ruchira Naved	Sociologist	Stress, work load, mental health
Anisur Rahman	MO, public health physician	Arsenic substudy
Motiur Rahman	Laboratory scientist, STD/RTI	BV intervention
Kuntal Saha	MO	Co-ordinator (2001-2002)
Rubina Shahen	MO (reproductive health)	Health economics evaluation
Nigar Shahid	Senior scientist	BV intervention, Lactation
Peter Kim Streatfield	Head, HDSU	Health & Demographic Surveillance
Yukiko Wagatsuma	Epidemiologist	Sonography
MA Waheed	Head, nutrition biochemistry lab	Laboratory assessments
Md Yunus	Senior scientist, public health	Matlab co-ordination

BRAC: Mushtaq Chowdhury, Zeba Mahmud (food supplementation programme)
Cornell University: Prof Kathleen Rasmussen (maternal nutrition), Prof Gretel Pelto (Ethnography), Prof J-P Habicht (nutrition epidemiology), Prof Ed Frongillo (nutrition epidemiology and biostatistics), Prof Jere Haas.
LSH&TM: Andrew Prentice (Co-PI, immune function), Sophie Moore (immune function), Andrew Collison (thymic ultrasound).
Cambridge University: David Dunger (foetal programming, gene-environment interaction)
Institute of Child Health, London: Sally Grantham McGregor (psycho-motor development)
University of Cambridge: David Dunger (foetal programming, gene-environment interaction)
Umeå university: Lars Lindholm (health economics).
UC Davis; Bo Lönnerdal (nutrition biochemistry)
London University: Graham Hitman (foetal programming, gene-environment interaction)

DESCRIPTION OF THE RESEARCH PROJECT

Hypothesis to be tested:

Concisely list in order, in the space provided, the hypothesis to be tested and the Specific Aims of the proposed study. Provide the scientific basis of the hypothesis, critically examining the observations leading to the formulation of the hypothesis.

The main hypotheses to be tested relate directly to the randomised study design and deal with functional outcomes beyond birth:

1. Women in the early assignment food supplementation group will have infants with higher attained weight and length than women in the usual assignment group.
2. The intervention with 30 mg Fe, 400 µg folic acid and 13 additional micronutrients (MuMS) will increase infant's weight, length, motor milestone and cognitive development, and enhance lymphoid tissue development and post-natal immune development, and decrease morbidity compared to the 60 mg iron + folate (Fe60F) and 30 mg iron + folate (Fe30F) micronutrient interventions.
3. There will be an interaction between food supplementation and multiple micronutrient supplementation such that those women who began food supplementation early and received MuMS will have infants with the highest attained weight and length, motor milestone and cognitive development, enhanced lymphoid tissue development and post-natal immune development, and show the lowest morbidity.
4. Food supplemented women of the mid- and lowest pre-pregnancy weights will show a larger increase of weight over the whole pregnancy cycle compared to women of highest pre-pregnancy weight. This will lead to a positive effect on the birth weight of the subsequent child, that is dependent upon the initial pre-pregnancy weight, the total number of days of food supplementation in pregnancy (higher dose more effect) and early or later start of supplementation (early start higher effect).
5. As was hypothesised already in the pregnancy-related protocol of this cohort there will be an interaction between the various amounts and types of supplementation and women's ability to extend the period of exclusive breast-feeding. In particular, women receiving food supplementation earlier or who have high total supplemental energy will be able to extend the period of EBF longer and with less decrease in maternal weight. Further, we hypothesise that the mentioned combination of nutrition interventions will influence micronutrient composition and thymic trophic factors in breast milk.

This study also provides the opportunity to evaluate how much exposure to the interventions is needed to obtain a maximal effect (dose-effect analyses).

The proposed research will validate the causal impact of these interventions and also evaluate their synergistic effects and cost-effectiveness. This research also will permit us to assess who benefits from the interventions, estimate efficacy and cost-efficacy of the interventions, provide insight into ways to improve participation in the future, and permit extrapolation of these findings to future interventions in other settings.

Although not being a primary objective, the HDSS system will provide full information on any deaths occurring within the infant cohort and allow for comparison of mortality between the supplementation groups. However, the power to detect smaller difference will be limited (see sample size calculations).

Background of the Project including Preliminary Observations

Describe the relevant background of the proposed study. Discuss the previous related works on the subject by citing specific references. Describe logically how the present hypothesis is supported by the relevant background observations including any preliminary results that may be available. Critically analyze available knowledge in the field of the proposed study and discuss the questions and gaps in the knowledge that need to be fulfilled to achieve the proposed goals. Provide scientific validity of the hypothesis on the basis of background information. If there is no sufficient information on the subject, indicate the need to develop new knowledge. Also include the **significance and rationale** of the proposed work by specifically discussing how these accomplishments will bring benefit to human health in relation to biomedical, social, and environmental perspectives. (DO NOT EXCEED 5 PAGES, USE CONTINUATION SHEETS).

This protocol shares the background with the MINIMat protocol (2000-025), that describes four combined interventions in pregnancy with a focus on effects on foetal growth, birth weight and maternal haemoglobin. The initiative emanates from the situation analysis showing that the frequency of low birth weight (LBW) in Bangladesh is as high as 50% (Arifeen S, 1997; Arifeen S, 2000; Goodburn and Chowdhury, 1994; Osendarp *et al*, 2000). Inasmuch as the occurrence of LBW reflects both the mother's historic and current nutritional status and affects the prognosis for infant health, growth and development, this is an alarmingly high statistic. Despite the success in Bangladesh in recent years of preventing unnecessary deaths of infants and young children from diseases such as diarrhoea, many underlying causes of illness remain--particularly inadequate breast feeding and poor maternal and infant nutrition.

One of the fundamental principles of the MINIMat design was to combine interventions that could have an effect on more than one contributing cause to the low birth weight situation in Bangladesh. The effect of combined interventions would theoretically be higher than that of single intervention effects added together. Randomised food and micronutrient interventions were combined, and an effort was also made to influence the high rate of pre-term delivery by a randomised treatment of a possible causative factor – asymptomatic bacterial vaginosis. For a comprehensive assessment of the effects of these combined interventions we should go beyond the immediate outcome during pregnancy and child birth. This follow-up protocol addresses functional outcomes on the maternal side during a whole pregnancy cycle, and on the child's side from birth to two years of age.

Rationale for studying the effects during a whole pregnancy cycle and on the birth weight of the subsequent child

Evidence from food supplementation trials conducted in developing countries is quite consistent across a variety of different kinds of food supplements: the more supplement a woman consumes, the bigger her baby. For a woman to consume more total food, she has to begin to accept supplementation earlier in pregnancy or consistently consume more food daily (Lechtig *et al.*, 1975; Kardjati *et al.*, 1988; Mora *et al.*, 1979). Further, the effect of the supplementation may be seen not only in the index pregnancy, but also into the next: compared to those who consistently consumed the least supplement in Guatemala, those who consistently consumed the most had second study infants who were 238 g larger than first study siblings (Villar and Rivera, 1988).

Results from Pakistan and Guatemala indicate that during a full reproductive cycle, a reduction in maternal weight is dependant on the level of pre-pregnancy weight. Women with the lowest pre-pregnancy weights (up to 42 kg) were hypothesised to preserve their own weight at the expense of foetal growth. Women with a moderately low pre-pregnancy weight (42-53 kg) lose weight to ensure foetal growth while those with a higher pre-pregnancy weight (53 kg and above) can both maintain their weight over a pregnancy cycle and ensure adequate foetal growth (Winkvist A, 1994; Winkvist A, 1998). Supplementation is likely to reduce the negative changes, that is, benefit the infant of moderately as well as severely malnourished women, and benefiting the moderately malnourished woman into the next pregnancy cycle. In Bangladesh , where the prevalence of malnourished women is high (Gopalan C, 1996), interventions to increase energy and protein intake in pregnancy – if not earlier – are urgently needed (Ceesay SM, 1997). The differentials in effect on birth weight depending upon maternal weight was recently confirmed in observational data from Bangladesh (Shaheen R, unpublished data).

Little is known about the effect of iron supplementation in pregnancy on post-partum iron and haemoglobin status, although some studies have claimed, that such interventions improve iron status and reduce anaemia prevalence also in the non-pregnant part of women in reproductive age (Stoltzfus RJ, 1998). Recently we have shown that iron supplementation to pregnant women had a dose-effect on haemoglobin concentration and iron

stores at 6 weeks post partum (Hyder Z, 2002). It is not known, if any effect of iron supplementation during pregnancy and puerperium on maternal haemoglobin and iron status remains even a year after child birth or later.

Rational for studying the effects on immune function and morbidity of the child

There is now substantial evidence, mainly from Europe and North America, to suggest that events during early life can influence an individual's future susceptibility to certain non-communicable diseases (NCDs) {Barker, 1994 #3}. The 'fetal origins' hypothesis states that cardiovascular disease and non-insulin dependent diabetes originate through adaptations that the fetus makes when it is undernourished. These adaptations, which include slowing of growth, permanently change the structure and function of the body {Barker, 1999 #540}. In addition to this, there is now preliminary evidence that susceptibility to infectious disease may also be programmed by events early in life. Adults born during or shortly after the nutritionally debilitating annual 'hungry' season in rural Gambia were found to have a maximal odds ratio of >10 for deaths between 25 and 50 years of age {Moore, 1997 #1; Moore, 1999 #534}. Since the majority of these premature adult deaths were from infections or infection-related disease, this finding led to the hypothesis that an insult occurring in early life and linked to season of birth, is disrupting the immune response resulting in premature mortality.

The hypothesis that immune function may be programmed by events early in life is supported by several pieces of evidence from the literature. Many components of the human immune system mature early in fetal life {Hayward, 1978 #665}, and maternal malnutrition has been observed to have greater effects on thymic and lymphoid tissue development than on other organs {Winick, 1966 #130; Owens, 1989 #345; Chandra, 1991 #339}. Such deficits in organ growth and development occurring *in utero* have been shown to be more serious and long-lasting than those caused by later malnutrition {Beach, 1982 #380; Chandra, 1991 #339}. In addition, there is evidence that low birth weight babies may have sustained impairment of immune competence as infants and children when assessed by various *in vitro* methods {Chandra, 1974 #666; Chandra, 1975 #388; Ferguson, 1974 #387; Victora, 1988 #332}, though such findings are not universal {Pittard, 1984 #667}. Increased susceptibility, following IUGR, to infections in childhood is also well known {Ashworth, 1998 #668} with hazards ratios for infectious deaths rising as high as 5.0 in Brazil {Victora, 1988 #332}. Furthermore, a study of adolescents participating in an ongoing longitudinal study in the Philippines has shown that prenatal undernutrition is significantly associated to reduced thymopoietin production, and growth in length during the first year of life was shown to be positively associated with adolescent thymopoietin production {McDade, 2001 #664}. In the same cohort, the predicted probability of mounting an adequate antibody response to a typhoid vaccine was lower in adolescents who were prenatally and currently undernourished (0.32) compared to adequately nourished adolescents (0.49-0.70) {McDade, 2001 #660}. The evidence linking adult immune function to birth size is limited so far to two published studies from Barker's group in Southampton linking disproportionate fetal growth to altered IgE concentrations in adult life {Godfrey, 1994 #141} and to auto-immune thyroid disease {Phillips, 1993 #64}. The precise mechanisms for any of these observations have yet to be described.

Ongoing studies by Prentice's group in The Gambia are attempting to define the biological mechanisms underlying the early-life programming of immune function. A prospective birth-cohort study of neonatal immune function and development has demonstrated seasonal effects on thymic size (measured by ultrasonography), with smallest thymuses found in infants both born and when measured in the hungry season, irrespective of infant weight {Collinson, 2002 #680}. In addition, there is evidence that this tracks within individuals up to the end of the first year of life. This difference in thymic size between the harvest and hungry season babies is greatest at 8 weeks of age, an age at which infants in this community are exclusively breast fed, have good weight, and have minimal exposure to infections. In addition, the $CD4^+/CD8^+$ ratio averaged over the first year of life was significantly lower for infants born in the hungry season and this difference was already apparent in cord blood where an unusually high level of double-positive $CD4^+/CD8^+$ T-cells might indicate a premature release of thymocytes in response to an environmental stress (AC Collinson, unpublished results).

Ongoing work in The Gambia continues to explore the biological mechanisms responsible for early-life programming of immune function. However, it is also of considerable importance to test the hypothesis in other ecological settings and to expand this programme of work. In this respect, the current collaboration has been initiated between ICDDR,B and the LSHTM/Gambian group to test the hypothesis that pre-natal malnutrition plays a role in programming later immune function within the MINIMat study. In addition, the proposed study will specifically explore possible influences of trophic or immunologically active human milk consitituents on thymic development and function.

Rationale for studying the effects on breast-feeding and lactation

As pointed out in the protocol for the MINIMat study a large percentage of infants in the world are not fed according to these recommendations. In Bangladesh, only 54 % of infants <4 months of age are exclusively breast-fed, while the median duration of partial BF is about 3 years (ACC/SCN, 2000). Therefore, there is a need to improve the duration of exclusive breast-feeding in Bangladesh, especially because it is this breast-feeding behaviour that is most associated with infant health and survival (ACC/SCN, 2000).

Several studies have demonstrated that breast-feeding promotion is effective in increasing the duration of exclusive breast-feeding, with interpersonal counselling being the crucial intervention (ACC/SCN, 2000; Albernaz et al., 1998). Breast-feeding promotion is understood to be one of the most cost-effective interventions for child health, comparable to immunisations, with important effects on reducing morbidity and mortality (WHO Collaborative Study Team, 2000). The timing of an intervention to promote exclusive breast-feeding is important so as to be able to positively affect mothers' decision-making, motivation and problem-solving, and persistence in the face of negative influences and obstacles. Inasmuch as exclusive breast-feeding declines sharply in the first few weeks after delivery, it is important to especially counsel mothers during pregnancy as well as right after delivery, and during the following first weeks (ACC/SCN, 2000). Work already completed in Bangladesh has shown that community-based peer counselling increases the duration of exclusive breast-feeding (Haider et al., 2000). Although mothers in Bangladesh are poorly nourished on average, their lactational capacity is presumed not to be severely impaired. Nevertheless, mothers' milk production is somewhat limited by their nutritional status and may be able to be increased through improvement in nutritional status (Brown et al., 1986). Consequently, interventions to improve nutritional status of mothers during gestation and lactation may have a synergistic effect with promotion of exclusive breast-feeding on both the duration of exclusive breast-feeding as such and the well-being of infants. This potential benefit for the well-being of infants needs to be studied along with the potential benefits and costs for mothers (Frongillo and Habicht, 1997). The research proposed here will provide a unique opportunity to examine these issues in a comprehensive manner, with attention to multiple maternal and infant outcomes as well as to cultural, social, behavioural, and biological factors.

Little is known about the effect of low maternal zinc intake on milk zinc concentrations during long exclusive breast-feeding. Animal studies suggest that zinc secretion may decrease (Beshgetoor D, 1997). The current MINIMat trial offers an opportunity to study if supplementation in pregnancy with multiple micronutrients including zinc alter the breast-milk output of zinc. Such longitudinal analysis based on randomised trial have recently been requested (King JC, 2002).

The observation that seasonal effects on thymic size were greatest in early infancy could suggest that breast milk has a specific trophic effect on the thymus. Breast-feeding may promote thymic growth, and it has been suggested that this is mediated by the transfer of immunological or trophic factors {Hasselbalch, 1996 #356; Prentice, 2000 #669}. A detailed study of breast milk antimicrobial factors in rural Gambian women found that in comparison with dry season samples, breast milk collected in the late rainy season contained 35% less IgA and IgG, and 20% less secretory component and lysozyme {Prentice, 1984 #430}. A slight fall in milk production during the rainy season compounded the decrease in daily production of these factors. A more recent study has confirmed the seasonality of breast-milk IgA levels in this community {Weaver, 1998 #429}. Breast milk may also be a medium for hormonal or cytokine signals. These may exert direct trophic effects on the thymus, or act indirectly via specific cells or cytokine networks of the infant immune system. Many such candidate factors have been identified in breast milk, including leptin, epidermal growth factor, transforming growth factors α and β, interleukin-1 (IL-1), IL-6, and other cytokines {Houseknecht, 1997 #670; Garofalo, 1998 #672; Hawkes, 1999 #671}. IL-7 appears to be essential to thymocyte development [Plum, 1996 #1004], and there is evidence that IL-7 reduces the rate of thymocyte apoptosis at the CD3-CD4-CD8- triple-negative stage. An increase in apoptosis of triple-negative thymocytes has been implicated in the age-related decline of thymopoesis {Andrew, 2001 #673}. Animal experiments have shown that cytokines can retain biological activity during passage through the gastrointestinal tract and may be taken up into the circulation {Wold, 1998 #674}. Leptin in particular may be implicated, since exogenous leptin has been shown to eliminate starvation-induced thymic atrophy in mice {Howard, 1999 #401}, and leptin concentration in breast milk is related to maternal nutritional status {Houseknecht, 1997 #670}. Although it is universally accepted that breast milk supports passive immunity, the extent to which trophic and immune factors in breast milk influence adaptive immune function remains to be established {Wold, 1998 #674}.

Rationale for studying the effects on infant growth and micronutrient status

Zinc is a constituent in several essential metalloenzymes with critical roles in metabolic functions. Zinc deficiency is widely prevalent in women and children in Bangladesh (Osendarp SJM, 2000; Sarker SA, 1985). The results of zinc supplementation trials during pregnancy on birth weight have been inconclusive (de Onis M, 1998). Two recent studies in Peru and Bangladesh did not show any effect on birth weight after maternal zinc supplementation (Osendarp SJM, 2000; Caulfield LE, 1999). A recent meta-analysis zinc supplementation trials in infants, however, has shown a small but highly significant effects of zinc on height and weight (Brown KH, 1988). Very little is known about the possible importance of interactions among several micronutrients on pregnancy outcome (Ramakrishan U, 1999). Recent work in ICDDR,B has shown that supplementation of women with zinc during pregnancy, while devoid of any positive effect on birth weight, resulted in reduced risk of watery diarrhea, dysentery, and impetigo in the infants during the first six months of life. These positive effects were observed in low but not normal birth weight infants (Osendarp SJM, 2001), i.e. the infants at greatest risk.

Maternal iron deficiency is wide spread in developing countries and is extremely common during pregnancy. Approximately three of every four pregnant women in South East Asia are anaemic, most of which is due to iron deficiency (UNICEF/UNU/WHO/MI, 1999). Infants born to mothers with iron deficiency anaemia are more likely to have low iron stores at birth (UNICEF/WHO, 1995), while iron supplementation of moderately anaemic pregnant women resulted in beneficial effects on the iron store of their infants (Pollitt E, 1993). The role of iodine in foetal and infant growth and development is well established. Maternal iodine deficiency during pregnancy has been reported to be associated with foetal growth retardation and impaired psychological development of infants (Hetzel BS, 1989).Even a milder form of iodine deficiency may cause psychological deficit in infants. Iodine supplementation in iodine deficient population during pregnancy has been shown to reduced stillbirth, infant mortality and improved motor performance in infants.

Vitamin A has a critical role in reproduction, immune function, vision and maintenance of cellular differentiation (Sommer A, 1996). Maternal supplementation with low dose vitamin A and or beta-carotene during the last two trimester of pregnancy has been shown to improve maternal vitamin A status and reduce pregnancy related mortality (West KP, 1999). Vitamin A status of newborns is marginal and those whose mothers have inadequate vitamin A intake appear to be at particular risk (Shirali GS, 1989; Greene HL, 1991). Vitamin A supplementation during pregnancy in population with marginal vitamin A status is likely to have beneficial effect on vitamin A status of their infants. Post-partum supplementation with vitamin A has been shown to improve infant vitamin A status and reduces risk for diarrhoeal morbidity (Rice AL, 1999; Roy SK, 1997) clearly indicating the importance of maternal vitamin A intake for infant vitamin A status and outcome.

Ample evidence exists that maternal micronutrient status plays an important role in the survival, growth, morbidity, immune function and psychomotor development of foetuses and infants. However, supplementation with single micronutrients is not always beneficial and might even be detrimental, most likely due to adverse or inhibitory effects on absorption of other micronutrients. Multiple micronutrient deficiencies often exist simultaneously in environments where maternal malnutrition is highly prevalent. Therefore combined interventions with multiple micronutrients with or without supplemental or additional energy and protein are likely to be more effective than single micronutrient interventions. Unfortunately, virtually no evidence is available on the effect multiple micronutrient supplementation during pregnancy on morbidity and growth of infants. Combined Interventions to Promote Maternal and Infant Health (MINIMat) study with the aim of determining the effect on birth weight and low birth weight of UNICEF's multiple micronutrient mix supplementation vs. iron and folate only with or without balanced energy and protein supplementation during pregnancy is currently ongoing. This study provides a unique and cost-effective opportunity to follow the infants born to these mothers and define the effects of maternal multiple micronutrient supplementation and their interaction with additional maternal energy and protein on infant morbidity and growth, and micronutrient status during infancy and early childhood.

Rationale for studying the effects on infant motor and cognitive development

Brain growth spurt occurs in the last trimester of pregnancy and early postnatal period (Levitsky DA, 1995). Low birth weight infants with pre- and postnatal growth faltering suffer from poor cognitive development, poorer academic achievements and productivity, as well as behavioural problems in childhood (Aylward GP, 1989; Richards M, 2001; Sorensen HT, 1997; Strupp JB, 1995). It should be noted, that low birth weight is not one entity, but includes combinations of intrauterine growth restriction and pre-term delivery with potentially different consequences for psycho-motor development.

The role of iodine during pregnancy and brain development is well established (Grantham McGregor S, 1999). A recent prenatal supplementation trial with zinc demonstrated a small negative behavioural effect in

infancy, where the authors speculated that the observed negative effect may be due to imbalances with other micronutrients secondary to competitive interactions (Hamadani JD, 2002). The knowledge base is weak and results are conflicting regarding the effect of combinations of food and micronutrient supplementation in pregnancy on motor and cognitive development (Waber DP, 1981; Joos SK, 1983; Freeman HE, 1980). The MINIMat prenatal supplementation trial with combinations of early or late start food supplementation and iron-folate or multiple micronutrients (including iron, zinc, vitamin A and iodine) offers an excellent opportunity to evaluate effects on the psycho-motor development of the child.

Research Design and Methods

Describe in detail the methods and procedures that will be used to accomplish the objectives and specific aims of the project. Discuss the alternative methods that are available and justify the use of the method proposed in the study. Justify the scientific validity of the methodological approach (biomedical, social, or environmental) as an investigation tool to achieve the specific aims. Discuss the limitations and difficulties of the proposed procedures and sufficiently justify the use of them. Discuss the ethical issues related to biomedical and social research for employing special procedures, such as invasive procedures in sick children, use of isotopes or any other hazardous materials, or social questionnaires relating to individual privacy. Point out safety procedures to be observed for protection of individuals during any situations or materials that may be injurious to human health. The methodology section should be sufficiently descriptive to allow the reviewers to make valid and unambiguous assessment of the project. (DO NOT EXCEED TEN PAGES, USE CONTINUATION SHEETS).

The research design and interventions are described in detail in the MINIMat protocol. This follow-up protocol focuses the post-natal functional outcomes. In summary, we evaluate the effects of four combined interventions among a single group of 3000 women in Matlab, Bangladesh, the well-established field site of ICDDR,B. An on-going surveillance program identifies pregnant women within 6-8 wk of conception. A government program managed by BRAC provides a food supplement to pregnant and lactating women that contains 600 kcal/d (6 d/wk) and a pill that contains 60 mg iron (Fe) and 400 mg folic acid daily. **Intervention 1:** We are randomly assigning women to receive advice to begin the food supplementation program (a) immediately after diagnosis of pregnancy (early care) or (b) at the time of their choosing (usual care). **Intervention 2:** Within each of these groups, we are randomly assigning women to receive a pill that contains (a) 30 mg Fe and 400 :g folic acid or (b) 60 mg Fe and 400 µg folic acid (usual care) or (c) 30 mg Fe, 400 µg folic acid and 13 additional micronutrients. **Intervention 3:** All women are being offered screening for Bacterial Vaginosis (BV). Within each of the 6 groups mentioned above asymptomatic BV-positive women are randomly assigned to (a) 250 mg metronidazole orally thrice daily for 7 days or (b) lactose tablets given with the same dose frequency. **Intervention 4:** We are randomly assigning all of the subjects to receive either (a) counselling for exclusive breastfeeding (EBF) or (b) a different health education message of equivalent intensity

Schedule of field activities after birth

The different field activities 0-24 months after birth are summarised in the schedule below.

MINIMat Infant schedule (Birth - 24 months)

		Months																									
	Birth	2 w	0 1	0 2	0 3	0 4	0 5	0 6	0 7	0 8	0 9	1 0	1 1	1 2	1 3	1 4	1 5	1 6	1 7	1 8	1 9	2 0	2 1	2 2	2 3	2 4
MOTHER																										
Activity Location	H/C	H	H	C	H	H	H	C	C	H	H	H	H	C			H			C			H			C
Weight	P			P				P						P												P
Morbidity	P	F																								
Placenta	P (at C)																									
Blood														P												
Breast milk				P				P						P												
Depression scale									P																	
Food security									P																	
CHILD																										
Activity Location	H/C	H	H	C	H	H	H	C	C	H	H	H	H	C/ H			H			C/ H			H			C
Anthropometry	P		F	P	F	F	F	P	P	F	F	F	F	P			F			P			F			P
Milestones					F	F	F	P	P	F	F	F	F	P			F			P						
Bayley PM									P																	
Bayley								P																		
Home inventory														F						F						
Language inventory														F						F						
Morbidity	P	F	F	P	F	F	F	P	P	F	F	F	F	P			F			P			F			P
Feeding		F	F	P	F	F	F	P	P	F	F	F	F	P			F			P			F			P
Thymus	S (at C)			S				S						S												
Blood	C (at C)			P*				P						P												
DTH response														P												
	Birth	2 w	0 1	0 2	0 3	0 4	0 5	0 6	0 7	0 8	0 9	1 0	1 1	1 2	1 3	1 4	1 5	1 6	1 7	1 8	1 9	2 0	2 1	2 2	2 3	2 4

H = home; C = Clinic; P = paramedic/nurse; F = field worker/interviewer; S = sonographer

* = subsample

Anthropometric measurements

The infant anthropometric assessment has already been approved by RRC/ERC as part of protocol 2000-025.

Infants will be measured by trained paramedic (if delivered at clinic) or field worker (if delivered at home) with SECA Electronic Infant Weighing Balance accurate to 10g. After 6 months of age the electronic scales UNISCALE will be used. These are accurate to 100 g. Length will be measured to the nearest 0.1 cm with locally constructed wooden length board. Head and chest circumference will be measured to nearest 0.1 cm using non-stretchable tape (TALC tape). All the measurements will be taken twice and the mean will be recorded. Measurements at birth will be taken within 72 hours of delivery, as already described in the MINIMat protocol. Subsequent measurements will be scheduled monthly up to 12 months and then three monthly up to 24 months. All measurements will be taken following standard procedures (Gibson RS, 1990).

Mothers weight will be measured at 2,6, 12 and 24 months after birth. All maternal weights will be measured with electronic scales (UNISCALE), which are accurate to 100 g.

Morbidity surveillance

Trained interviewers will collect morbidity data of the infant by a one-week recall on a monthly basis, specifically probing for symptoms of diarrhoea, fever, acute respiratory illness and skin infection. Additionally, severe diseases requiring hospitalisation will be registered. After 12 months morbidity will be assessed every 3 months. Further, the morbidity of mothers will be registered by interviews at 72 hours after birth and 2 weeks after birth.

Feeding pattern and dietary intake of infants

Through interviews at around 72 hours after birth and 2 weeks after birth the introduction of breast feeding, use of pre-lacteal feeding, use of colostrum as well as any complementary fluids and foods will be mapped. Thereafter, on a monthly basis to 12 months of age, followed by quarterly interviews, the introduction of any new fluids or food items to the infant's diet will be registered. In addition, quantitative assessment of dietary intake of

infants will be done at 3, 6, 9 and 12 months of age using 24-hour dietary recall performed by trained field worker in the home environment.

Motor milestone assessment

This assessment has already been approved for infancy by RRC/ERC as part of protocol 2000-025.
Trained field workers will interview mothers and observe the child's achievement regarding motor milestones. This assessment will be performed at home (at the clinic on some occasions), and be performed on a monthly basis from 3 months of age, followed by assessment every third month from 12 -18 months. This assessment will be combined with the anthropometric measurements.

Psycho-motor development assessment

At 7 months of age trained psychologists will assess the infant's problem solving capacity by using the "two means-end one step problem-solving test ", Willats test (Willats P, 1998). The test involves pulling a cloth to retrieve a toy placed on the table. Infants at 7 months begin to use intentional means-end behaviour to solve the problem. They pull the cloth instead of playing with it, maintain fixation on the toy at the far end, and retrieve it. They will also assess the psycho-motor development and behaviour of these infants by using Bayley's psychomotor scale (Bayley N, 1993) and a modified version of Bayley & Wolke behaviour ratings (Wolke D, 1990) at 7 and 18 months. This test includes vocalisation, co-operation with test procedure, activity level, emotional tone and response to examiner. These scales have been used before in Bangladesh and showed good inter-observer reliability.

At 18 months the psycho-motor development will be assessed by Bayley scale of infant development II (Bayley N, 1993). The two sub-scales are mental and psychomotor development indices. Good inter-observer reliability has been obtained when the test previously was used in Bangladesh. These assessments will be performed at the Matlab sub-centres and the female testers will be unaware of intervention groups.

Home observation for measurement of environment

Field assistants will collect information about the child's situation at home, using a modified version of Betty Caldwell's home inventory, which was modified for Bangladesh in a previous study by this research group. The observation will be made at 12 and 18 months.

Language inventory

Children's ability to understand and use the language will be assessed by a modified version of the MacArthur's communicative development inventory. The inventory will be translated, piloted and field tested before start of field work. Inter-observer reliability will be assessed. The assessment will be done at 12 and 18 months.

Thymic ultrasound

This assessment has already been approved by RRC/ERC as an addendum to protocol 2000-025.
Thymic size will be measured by ultrasonography using a Toshiba SSA 320A Justavision-200 portable machine together with a PVF-745F sonographic micro-probe. All infants born into the MINIMat study will have a measure of thymic size taken at 8, 24 and 52 weeks of age. Additionally, all infants born at the four sub-centres and recruited into the in-depth component of the study will have a measurement made during the first 24-48 hours of life.

Thymic size will be measured by paramedic staff trained in this technique using a validated method in which the transverse diameter of the thymus and the sagittal area of its largest lobe are multiplied to give a volume-related thymic index {Hasselbalch, 1996 #357}. Thymic index has been shown to correlate with thymus weight at autopsy {Hasselbalch, 1996 #357}. Infants will be scanned in the supine position, using a trans-sternal approach. Ultrasonography will not be performed while the infants are crying. Each measure will be performed in triplicate. This technique is safe, non-invasive and takes a few minutes only. Training, validation and quality control of the technique will be performed by Dr Sophie Moore and Dr Andrew Collinson who performed the thymic ultrasound measurements in The Gambian work, in collaboration with Dr Yukiko Wagatsuma, who is the responsible scientist for the foetal ultrasound assessment in the MINIMat study.

Blood samples from mothers

Hb concentration will be assessed from a drop of venous blood at approximately 12 months after delivery by use of HemoCue® system. The accuracy of the HemoCue® machines will be checked daily using control cuvettes.

4 mL of blood will be collected from venipuncture in trace-element-free lithium heparin tubes at approximately 12 months after delivery. The tubes will be protected from light and heat and will not be allowed to stand or be shaken. Plasma will be separated and frozen at either -20 or -70 °C depending on period of storage. Plasma ferritin will be assessed using immuno-radiometric assay (R & D Systems, Minneapolis, MN, USA). Soluble transferrin receptors will be assessed by an enzyme immunoassay (double-sandwich method) (Ramco Laboratories, Houston) (Flowers et al., 1989). Vitamins will be assayed in HPLC, while folate will be tested with a bioassay. CRP will be analysed by immunoturbidimetry using a Roche kit in a Hitachi autoanalyzer. All trace elements will be measured using atomic absorption spectrophotometry.

Blood samples from infants

Cord blood samples from the umbilical vein will be collected from infants delivering at the Matlab sub-centres (approximately 30% of the cohort) and two lithium heparin tubes of 4 ml will be filled. At 8, 24 and 52 weeks of age a 4 ml sample of venous blood will be collected from each infant in this sub-sample (circa 700 infants) by a trained research physician/nurse. Further, from all infants (about 2250 infants including the 700) venous blood samples will be collected at 6 months.

Hb concentration will be assessed from a drop of venous blood at 6 months after delivery by use of HemoCue® system. Plasma ferritin will be assessed on the 6-month sample using immuno-radiometric assay (R & D Systems, Minneapolis, MN, USA). P-zinc will be assessed by atomic absorption spectrophotometry.

One aliquot of lithium heparin whole blood from the sub-sample at birth (cord blood) and at 8, 24 weekss and 52 weeks of age will be transported at room temperature to Dhaka for processing by FACS.

Lymphocyte populations and sub-populations will be measured by three colour fluorescence analysis using a FACSort flow cytometer (Becton-Dickenson). Analysis will be performed on blood samples collected at birth (cord blood), 8 weeks, 24 weeks and 52 weeks of age.

It is anticipated that the following panel of monoclonal antibodies will be used in the FACS analysis: $CD4^+$ (T-helper cells), $CD8^+$ (cytotoxic T-cells), $CD3^+$ (Total T cells), CD45RA (naïve T-cells), CD45RO (memory T-cells), CD69 (activation marker), Il-7, IFN-α, and Il-4.

Breast milk samples

Samples of breast milk will be collected from lactating mothers at 8, 24 and 52 weeks post-partum. Samples will be collected using a standardised procedure; small samples of milk will be obtained from both breasts of each mother by maternal manual expression. A study in The Gambia using milk of women collected immediately before and after a feed demonstrated no significant differences in the concentrations of any immunoprotein between the beginning and end of a feed {Prentice, 1984 #452}. Similarly, no consistent diurnal variation was observed in subjects studied over a 24 hour period {Prentice, 1984 #452}. The stage of feed and time of day for the collection of milk samples will therefore not be considered. Left and right breast milk samples from individual mothers will then be pooled for the purpose of analysis.

Samples will be transported to the Matlab laboratory and frozen (-20°C) prior to transfer to Dhaka. Lactoferrin and Il-7 will be measured in extracted breast milk samples using quantitative colorimetric sandwich ELISA (R&D Systems, Minneapolis, MN). Secretory IgA will be measured by the standard method (RR, 2002) using a standard IgA of known concentration (Sigma, St Louis).

Assessment of micronutrients in breast milk will be performed. Details are still being discussed.

Breast milk and plasma leptin concentrations

The adipocyte-derived hormone, leptin, has cytokine-like function and may mediate the effects of starvation on immunity {Lord, 1998 #60; Howard, 1999 #401}. Mice with congenital leptin deficiency (*ob/ob*) have small hypocellular thymuses and impaired cellular immunity {Howard, 1999 #401}. In humans leptin influences the differentiation of naïve and memory cells *in vitro* {Lord, 1998 #60; Martin-Romero, 2000 #625}, and genetic leptin deficiency has been associated with an ill-defined susceptibility to infection {Ozata, 1999 #565}. Recent studies have indicated that the placenta provides a source of leptin for the growing fetus, and this placental leptin might be a growth factor in intrauterine fetal development {Ben, 2001 #675; Buchbinder, 2001 #676}.

In the current study breast milk leptin levels will be assessed in milk samples collected at 8, 24 and 52 weeks post-partum (see section III for details). In addition, plasma leptin levels will be measured in plasma samples collected at birth (cord blood) and 8, 24 and 52 weeks of age. Leptin concentrations in both breast milk and plasma samples will be measured using a well-characterised commercially available ELISA (Quantikine ELISA, R&D Systems, Minneapolis, MN).

Placenta samples

During normal pregnancy, a predominance of Th2 type cytokines prevails and are considered to protect the fetus. Animal experiments suggest that an increase of Th1 type cytokines may instead have deleterious effects. A recent study from Hahn-Zoric *et al* has shown that placentas from infants born with IUGR have significantly higher Il-8 and significantly reduced Il-10 mRNA than from normal infants {Hahn-Zoric, 2002 #677}. It is therefore possible that reduced Il-10 in the placenta is involved in the pathogenesis of IUGR, and studying cytokine levels in placental tissue will provide essential information regarding the fetal immune micro-environment and its effect on fetal and infant development.

Following delivery, placental weight will be measured after draining all placental blood, removing obvious clots, trimming the amnion and the cord, and trimming the chorion and cord to the placental. Placental tissue samples will then be collected into three separate tubes for analysis.

Delayed-type hypersensitivity (DTH) response

A delayed type hypersensitivity response will be made at 52 weeks of age using tuberculin antigens (details) applied into the flexor surface of the forearm. Reactions will be measured 48 hours later, and a transverse measurement of induration of 5 mm or greater will be considered as positive.

Depression scale, food security

A short scale for assessment of depression (SRQ 20) was used during pregnancy and will be used at 7 months (at the time of the first psychomotor assessment). A food security questionnaire was previously developed and evaluated for use in pregnancy. This instrument will also be used 7 months after delivery.

Costing data

The project will include health economics evaluation of the interventions. This will include costing of the interventions, cost-effectiveness analyses, and evaluation of incremental costs and benefits for combinations of interventions). Data on costs will mainly be collected by prospective micro-costing by the project personnel administering the interventions. That is, the details of all input costs will be collected and recorded. Estimates of possible savings in health care will be collected. Value of the gains will be assessed by a "willingness-to-pay" survey. The indirect costs will be equal to the value of production lost due to participation in the program. The resources needed for implementation of the intervention and the effects caused by the intervention will be identified, measured and valued. Resources will be valued in monetary units, effects will be measured in natural and appropriate physical units, and indication on value will be given by a ratio between costs and effects (C/E) measured in non-monetary units. Details of the planned data collection and analyses are presented in the MINImat protocol (2000-025), but effect data will be extended by the measurements described in this follow-up protocol.

Time plan

Study component	*2003*	*2004*	*2005*	*2006*
Base study up to birth				
Follow-up of mothers to next birth				
Lactation, breast milk, micronutrients				
Growth and micronutrients to 24 m				
Motor, cognitive development to 24 m				
Immune function, thymus size to 12 m				

Sample size calculations

Overall (unless otherwise stated) we assume that the power should be 0.90 (Type II error rate of 0.10) with testing at 0.05 (Type I error rate), and estimate the sample size needed for the minimum important difference (i.e., the smallest difference that is substantively important) given the expected variation. The calculations have accounted for 5% refusal, 11% loss during pregnancy and 9% loss during infancy due to death and out-migration. Thus, at 12 months of age 2250 infants (originally 3000 recruited pregnant women) are expected to remain in the study.

Follow-up of mothers into next pregnancy and child birth

In the current cohort of 3000 women births begun in May 2002, and the last birth is expected to take place in early 2004. This results in a median follow-up period after delivery to end of 2006 of 46 months. According to HDSS data from Matlab 30% of women delivering a baby have delivered a new baby after 46 months, i.e. 900 out of the original cohort have given birth to a new baby within the planned follow-up time to end of 2006. A two group t-test with a 0,050 two-sided significance level will have 90% power to detect the difference between a later start food supplementation mean of 2500 g and an early start supplementation mean of 2587 g, a difference in means of 87 g, assuming that the common standard deviation is 400 g, when the sample sizes in the two groups are 450 and 450, respectively (a total sample size of 900). However, if assuming that the main effect into next pregnancy is obtained in the mid-part of the distribution of mothers' pre-pregnancy weight (e.g. in the mid third of the distribution), differences of 150 g would be possible to show. We have previously considered 70 g to be the minimum important difference in birth weight (outcome of the index pregnancy).

Weight and height of the women (who delivered live births in their previous pregnancy) will be measured at 14 wks in their next pregnancy and at the same time 5.5 ml venous blood will also be collected at 14 wks of their pregnancy and birth weight of their newborns will be measured. Breastfeeding pattern will be assessed by home based interview within 72 hours of delivery, 2 weeks after delivery and thereafter on a monthly basis upto 12 months.

Considering the ability to demonstrate differences in haemoglobin 1 year after delivery of the index child, a two group t-test with a 0,050 two-sided significance level will have 90% power to detect the difference between any two of the three micronutrient supplementation groups of 2 g/l, assuming that the common standard deviation is 12 g/l when the sample sizes in the two groups are 450 and 450. If considering different levels of compliance, e.g. contrasting a lower third in the distribution of micronutrient intake against the highest third a difference in 4 g/l would be detected. A difference of 5 g/l is considered significant from a public health point of view.

We will also collect cord blood samples and respective placental tissue specimens from delivery. Following delivery, placental weight will be measured after draining all placental blood, removing obvious clots, trimming the amnion and the cord, and trimming the chorion and cord to the placental. Placental tissue samples will then be collected into three separate tubes for further analysis. Cord blood samples will be collected in heparinized tubes (20 ml), plasma and mononuclear cells will be separated for further analysis. We will study the expression pattern of cytokines in placental tissue that may provide essential information regarding the fetal immune micro-environment and its effect on fetal and infant development. Very preliminary data from the 1st pregnancy indicates that supplementation with 60 mg Fe leads to significantly increased numbers of macrophages and a marked reduction in neutrophil counts and pro-inflammatory cytokine expression in the placental tissue indicating increased immune surveillance and reduced inflammatory responses. A significant increase in plasma leptin levels in cord blood was observed in the 60 mg Fe group compared to the other two groups and were positively associated with birth weight. Mononuclear cells will be analysed for phenotypes of lymphocytes: $CD4^+$ (T-helper cells), $CD8^+$ (cytotoxic T-cells), $CD3^+$ (Total T cells), CD45RA (naïve T-cells), CD45RO (memory T-cells) and CD69 (activation marker).

Exclusive breast feeding

The sample size is sufficient to demonstrate differences of 15% in exclusive breast feeding prevalence between any two of the 2x3x2 = 12 intervention groups.

Infant growth and micronutrient status

The sample size will allow to demonstrate a difference between any of the 2x3x2=12 intervention groups in attained weight- or height-for-age Z-scores of 0.25.

Similarly, differences in haemoglobin at 12 months of 4 g/L could be detected.

Motor and cognitive development

A two group t-test with a 0,050 two-sided significance level will have 90% power to detect the difference in development quotient between any two of the six intervention groups of 3, assuming that the common standard deviation is 12, when the sample sizes in the two groups are 375 and 375, respectively (a total sample size in the six groups of 2250). However, if contrasting low- and high-compliance groups of micronutrient intake (dose-effect analysis) the sample size would suffice to demonstrate differences of 5 (125 in each strata). Differences of five are considered to be the minimum important difference from a public health point of view.

Preliminary Findings

Table. Semiquantitative expression of immunostaining in placental tissue from women supplemented with various micronutrient formulations.

Study Groups	30 mg Fe + folic acid	60 mg Fe + folic acid	P value	MUM + 30 mg Fe + folic acid	P value
	Placental tissue				
CD3	15.5 ± 4.3	10 ± 2.2	0.64	9.46 ± 2.1	0.84
CD8	8 ± 3.4	4 ± 1.1	0.24	3.7 ± 0.9	0.8
Macrophages	4.9 ± 1.5	9.4 ± 2	0.08	3.3 ± 1	0.03*
Neutrophils (MPO)	16.4 ± 2.2	18.4 ± 2.4	0.4	17.2 ± 2	0.7
TNF-α	0.56 ± 0.29	0.64 ± 0.32	0.62	1.24 ± 0.54	0.8
IFNγ	0.96 ± 0.29	0.86 ± 0.3	0.47	0.54 ± 0.24	0.44
IL-1β	0.4 ± 0.11	0.11 ± 0.02	0.02*	0.44 ± 0.16	0.1
	Cord blood plasma				
Leptin, ng/ml	3.35 ± 0.35	4 ± 0.35	0.06	3.3 ± 0.30	0.01

There was a significant increase in the number of macrophages in the placental tissue in the 60 mg Fe group compared to the MUM-groups. The difference between the 60 mg Fe- and the 30 mg Fe-groups were not significant. Expression of the pro-inflammatory cytokine IL-1β was significantly reduced in the 60 mg Fe-group compared to the 30 mg Fe-group. The results indicate that there is increased immune surveillance and reduced inflammatory responses at the local site in the placenta.

Both Th1 (IFN-γ, IL-2) and Th2 types (IL-4, IL-10) of cytokines were studied by immunohistochemical staining, however only IFN-γ could be detected in measurable levels in the placental tissue.

Immune function sub-study

In the proposed study there are two separate types of intervention: food supplements either with early or later start in pregnancy and one of 3 micronutrient supplementation regimes. The subjects will be randomised to equal sized food supplementation groups within which a third will be randomised to each of the micronutrient groups. There are also several outcomes including weight, thymic size and lymphocyte population structure at birth and various time points up to one year of age. Initially the impact of both types of intervention, along with other relevant covariables, will be analysed separately for each outcome and time point, using multiple regression. In the case of the three micronutrient groups we will look at the two independent contrasts: (i) vs (ii) and (ii) vs (iii). This analysis will also allow us to investigate the interaction between protein-energy and micronutrient supplementation and other covariables. We will then perform a multi-level analysis to investigate influences on changes with age.

Our sample size calculations are based only on tests of difference between the main effects of supplementation at a single time point. We aim to arrange that the test of each type of supplementation for each outcome and time point should be capable of detecting 1/3 of a standard deviation for the variation of the outcome variable on 90% of occasions [e.g. using thymic size data from Gambian infants: for log(thymic size) sd/3=0.223/3=0.074 or equivalent to about 8% of the mean thymic size]. This should give us sufficient leeway to detect reasonably small differences between groups even if a sizeable proportion of the variance between individual outcome measurements is due to random "within-infant" fluctuation or measurement error (rather than genuine difference between children). E.g if 50% of the variance is due to error then sd/3 is equivalent to $\sqrt{(2\sigma)}/3$ or 0.47σ, where σ is the standard deviation of the genuine variation between infants. Thus each test must meet very similar criteria and we need only consider the least powerful, namely the difference between micronutrient groups since these have the smallest group sizes.

The sample size for each test was calculated using the usual formula:

$$N = 2\{\sigma/\Delta\mu \,.\, [\Phi^{-1}(1-\alpha/2) + \Phi^{-1}(\beta)]\}^2 ,$$

where $\Phi^{-1}(.)$ is the inverse normal distribution function, σ is the within-group standard deviation, $\Delta\mu$ is the difference in mean between groups, N is the sample size and α and β are the significance level and power respectively. Substituting values of $\alpha=0.05$ and $\beta=0.9$, $\Delta\mu/\sigma=0.333$ this reveals that we require approximately 200 per groups, i.e. a total of 600 deliveries.

Mortality

Although not being a primary objective, the HDSS system will provide full information on any deaths occurring within the infant cohort, as well as a cause of death through a verbal autopsy procedure. The sample size would suffice to demonstrate a difference in infant mortality rate of 25/1000 (e.g. the difference between 40/1000 and 65/1000) between the MuMS group and the iron-folic acid groups.

Facilities Available

Describe the availability of physical facilities at the place where the study will be carried out. For clinical and laboratory-based studies, indicate the provision of hospital and other types of patient's care facilities and adequate laboratory support. Point out the laboratory facilities and major equipment that will be required for the study. For field studies, describe the field area including its size, population, and means of communications. (TYPE WITHIN THE PROVIDED SPACE).

The Matlab field study area offers excellent facilities for this study. The Health and Demographic Surveillance System, is a regularly updated demographic information system on 210,000 population and can provide much of the data required for this study. The existing ICDDR,B field data collection staff in Matlab offers a pool of highly experienced and trained individuals to choose from. Both the Matlab and Dhaka-based data processing units of the Public Health Sciences Division have long experience in handling both longitudinal and special project data. The Sub-Centres are equipped with ultrasonography equipment and have trained staff for the thymic ultrasound. Matlab Centre has a supporting laboratory for handling of specimen, storage in freezers, and transport of samples to the Dhaka laboratory, when needed. The Immune laboratory in Dhaka has the needed equipment and staff for the planned analyses.

Data Analysis

Describe plans for data analysis. Indicate whether data will be analyzed by the investigators themselves or by other professionals. Specify what statistical software packages will be used and if the study is blinded, when the code will be opened. For clinical trials, indicate if interim data analysis will be required to monitor further progress of the study. (TYPE WITHIN THE PROVIDED SPACE).

For the blinded randomisations (micronutrients) the code will be opened after the primary analyses with birth weight, foetal growth and maternal haemoglobin. The analyses with the functional outcomes in infancy and during the follow-up of the mother will, however, be performed with the original codes in order to avoid biases in the analytical approach.

This study is designed as a randomised, controlled experiment with longitudinal follow-up. Women are randomly assigned to 1 of 12 cells of a 2x3x2 complete factorial design. Compliance to the interventions will be carefully assessed permitting evaluation of both efficacy and effectiveness of single interventions as well as for combinations of them.

Effectiveness will be assessed by "intention-to-treat" analysis of the outcomes. This analysis includes all subjects randomised into each group, even if some of those subjects did not comply with the conditions of the group. General linear models (i.e., analysis of variance and regression) with interactions will be used with continuous outcomes such as weight and haemoglobin values. Logistic regression will be used with binary outcomes such as rates of anaemia. Proportional hazards regression will be used with outcomes that capture time to an event such as duration of EBF. Poisson regression may be used to model morbidity outcomes. In all analyses, standard regression diagnostics will be done to evaluate model assumptions, including examining distributions, performing any needed transformations, and examining overall fit, residuals, and leverage. The proportionality assumption of the proportional hazards regression will be evaluated using plots of the product-limit estimator, residuals, and modelling using time-varying covariates. Inasmuch as some data will be collected at multiple times, static, developmental curve, and dynamic approaches for longitudinal analysis will be used.

Compliance information can also be used to estimate the dose-response to the biological intervention (e.g., more supplemental food). Dose-response estimates based on compliance information are subject to potential bias because compliance can be confounded by other biological or psychological factors that are related to the outcomes. Many of these will be known from our analyses of compliance and taken into account. We will test for lack of bias by showing that estimates of effectiveness derived from the dose-response curves is similar to that using the "intention-to-treat" analyses. Estimating efficacy from the dose-response curves requires not only that the curves are unbiased but also that they must properly model for changes in efficacy. Thus the relationships between compliance and outcomes may not exhibit straight lines, so a non-linear or threshold model may be most appropriate for some outcomes. This is certainly the case for the nutritional supplements that have less impact at higher doses as nutrition improves (Ekstrom et al., 1996, 1999). For the same reason individuals with different levels of initial deficiency will respond differently to a same dose and thus modify the effects of the intervention.

Ethical Assurance for Protection of Human Rights

Describe in the space provided the justifications for conducting this research in human subjects. If the study needs observations on sick individuals, provide sufficient reasons for using them. Indicate how subject's rights are protected and if there is any benefit or risk to each subject of the study.

Women are being enrolled in the pregnancy part of the study after giving their informed consent. At birth (if it occurs at the sub-centre, female *Paramedics* will obtain written informed consent for this continued follow-up (see written consent form, Appendix 1) for collecting biological samples, for the infant to undergo thymic ultrasonographic examination and for anthropometric follow-up and interviews.

Any enrolled woman may withdraw from the study at any point without affecting her access to and use of routine ICDDR,B services. She may also withdraw from any particular component of the study without affecting her participation in other components. For example, she may refuse to give blood or allow utltrasonagraphic examination. Confidentiality of information will be strictly followed, and access to data forms will be strictly limited.

In addition to ethical review at ICDDR,B, ethical permission will also be obtained for the Immune component from the Research Ethics Committee, London School of Hygiene and Tropical Medicine, UK.

Use of Animals

Describe in the space provided the type and species of animal that will be used in the study. Justify with reasons the use of particular animal species in the experiment and the compliance of the animal ethical guidelines for conducting the proposed procedures.

Not applicable

Literature Cited

Identify all cited references to published literature in the text by number in parentheses. List all cited references sequentially as they appear in the text. For unpublished references, provide complete information in the text and do not include them in the list of Literature Cited. There is no page limit for this section, however exercise judgment in assessing the "standard" length.

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Dissemination and Use of Findings

Describe explicitly the plans for disseminating the accomplished results. Describe what type of publication is anticipated: working papers, internal (institutional) publication, international publications, international conferences and agencies, workshops etc. Mention if the project is linked to the Government of Bangladesh through a training programme.

Early findings will be disseminated through short reports and working papers. Important results and conclusions will be disseminated through working papers, journal articles, policy reports and presentations at national, regional and international conferences and meetings.

Collaborative Arrangements

Describe briefly if this study involves any scientific, administrative, fiscal, or programmatic arrangements with other national or international organizations or individuals. Indicate the nature and extent of collaboration and include a letter of agreement between the applicant or his/her organization and the collaborating organization. (DO NOT EXCEED ONE PAGE)

The project involves a vast number of scientist from the different divisions at the Centre and collaborating partners in Bangladesh and abroad. Extensive consultations and meetings have preceded the development of the project plan. On the first pages the roles of the different scientists are defined. Below the main collaborations are listed.

BRAC: Mushtaq Chowdhury, Zeba Mahmud (food supplementation programme)
Cornell University: Prof Kathleen Rasmussen (maternal nutrition), Prof Gretel Pelto (Ethnography), Prof J-P Habicht (nutrition epidemiology), Prof Ed Frongillo (nutrition epidemiology and biostatistics), Prof Jere Haas.
LSH&TM: Andrew Prentice (Co-PI, immune function), Sophie Moore (immune function), Andrew Collison (thymic ultrasound).
Cambridge University: David Dunger (foetal programming, gene-environment interaction)
Institute of Child Health, London: Sally Grantham McGregor (psycho-motor development)
University of Cambridge: David Dunger (foetal programming, gene-environment interaction)
Umeå university: Lars Lindholm (health economics)
UC Davis: Bo Lönnerdal (nutrition biochemistry)
London University: Graham Hitman (foetal programming, gene-environment interaction)

ICDDR,B: Centre for Health and Population Research

Combined Interventions to Promote Maternal and Infant Health: Effects Over a Pregnancy Cycle and on Children 0-24 Months

WRITTEN CONSENT FORM

Thank you for participating in the study during pregnancy. We would like to invite you to continue to participate in the study even after child birth. I am sure you remember why we do this study, but let me repeat some of the information for your benefit. Good maternal nutrition and treatment of infection during pregnancy are very important for the health and well being of the mother and her baby. Poor maternal nutrition and infection during pregnancy are very common in Bangladesh, as in Matlab, which results in lack of energy/protein, vitamins and minerals. Because of this, a lot of illnesses and deaths take place among mothers and their babies.

ICDDR,B in collaboration with the Government of Bangladesh, UNICEF and collaborating universities in the United States and Europe is undertaking a study to improve maternal and infant nutritional status. You have participated in this during pregnancy, and it has focused the ongoing feeding program, tablets with vitamins and minerals, investigation regarding vaginal infection and advice regarding breast feeding. The "Pushti" program continues also after birth, you have received tablets with vitamins and minerals to take for some more months, and you will continue to receive either counselling to help you with breast-feeding of your baby or health education on care for yourself and the baby. We are now interested to study to what extent these interventions are benefiting your health and your child's health and further development.

[*Only when delivering at sub-centre*: We will collect two tubes of blood from the cord (not from you or your child) and we will also take a small piece of the placenta in order to examine health conditions in the placenta. We will also take 3 ml of blood in a tube from your child's veins at three different occasions during the first years in order to examine the effects of the food supplementation and the micronutrient tablets you received during pregnancy. We will examine the haemoglobin concentration on one of these occasions and inform you about the result. Other results will not be reported back, and we ask for your permission to use it for scientific purposes.]

[*Only when not delivering at sub-centre, during the 7-10 day home visit*: We will also take 3 ml of blood in a tube from your child's veins at 6 months in order to examine the effects of the food supplementation and the micronutrient tablets you received during pregnancy. We will examine the haemoglobin concentration and inform you about the result. Other results will not be reported back, and we ask for your permission to use it for scientific purposes.]

You are familiar with ultrasound examination. We will examine your child with ultrasound on 3-4 occasions, and see how thymus, an organ that is involved in the defence against infections, is developing. This examination takes a few minutes and is not causing any harm for your child.

We will continue to measure weight and other body measurements on your child and also, for a few times, even your weight. We will also ask questions about your health and your child's health, feeding and development. On three occasions during the first years we will observe how your child advances in movements and in play.

We will also collect 5.5 ml of blood (about a teaspoonful) from your veins. We will test this blood for anaemia, and tell the result. Other results will not be told, and we ask for your permission to use it for scientific purposes. We will also ask you to get a portion of breast milk on three occasions, for analysis of effects of the food and micronutrient supplementation.

We assure you that we shall maintain the confidentiality about the information we collect from you. All records from this study at the Matlab Diarrhoea Hospital or the Dhaka offices of ICDDR,B will be kept private and in a locked location. Only people doing the study will be able to look at them. Any study records that are taken from ICDDR,B will not have any of the names of who took part in the study.

Your participation is absolutely voluntary. You are at liberty to withdraw from the study at any time during the study without any penalty or change in the routine care you or your child receives. If you decide not to take part in these parts of the study, it will not change the care you, your child or your family receives from ICDDR,B in any way. You will still receive our routine care and necessary support and treatment.

You may ask any questions regarding the study and I shall be happy to answer them for you. If you have any problems or questions you can contact your home health care worker, or contact Matlab Hospital of ICDDR,B or Dr. Lars Ake Persson at the following phone number at any time: 988 5155 (Dhaka).

- Do you have any questions? Yes No
- Do you agree to participate in this study? Yes No

Signature of the witness
(Paramedic) Date: _____

Signature/thumb impression of pregnant woman

Check List

After completing the protocol, please check that the following selected items have been included.

1. Face Sheet Included [✓]
2. Approval of the Division Director on Face Sheet [✓]
3. Certification and Signature of PI on Face Sheet, #9 and #10 [✓]
4. Table on Contents [✓]
5. Project Summary [✓]
6. Literature Cited [✓]
7. Biography of Investigators [✓] PI
8. Ethical Assurance [✓]
9. Consent Forms [✓]
10. Detailed Budget [✓] Summary budget

External reviews

The psycho-motor development component was reviewed as pert of Dr Fahmida Tofails preparations for her PhD work and changes were included.

The Immune component was externally reviewed, see attached comments. Further it was extensively reviewed and discussed within Dr Prentice's group.

Most aspects regarding the other components were already included in the previous protocol (2000-025), although now being specified in time.

Detailed Comments:

Please briefly provide your opinions of this proposal, giving special attention to the originality and feasibility of the project, its potential for providing new knowledge and the justification of financial support sought; include suggestions for modifications (scientific or financial) where you feel they are justified.

(Use additional pages if necessary)

Title: Pre-natal programming of immune function in rural Bangladeshi children

PI: Rubhana Raqib Lars Åke Persson

Reviewer: Lars Hanson

This application concerns a most up-to-date and relevant research problem: can fetal events program for future disease.

The observations made by Prof. Prentice´s group in the Gambia of the increased adult mortality linked to the season of birth provides a possible approach to illumination of the problem The proposed cooperation within the research project already planned within the Matlab offers excellent opportunities which are well taken care of in this proposal.

The senior researchers involved are very competent and experienced in the field and this becomes obvious from the planning. I can really not come up with any negative criticism or suggestions of improvements. It is a most important, well planned research project on a very significant problem directed by some of the best researchers in the field.

I will be awaiting the results with great interest.

Title: Pre-natal nutritional programming of immune function in rural Bangladeshi children.

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score High	Medium	Low
Quality of project	X		
Adequacy of project design	X		
Suitability of methodology	X		
Feasibility within time period	X		
Appropriateness of budget	X		
Potential value of field of knowledge	X		

CONCLUSIONS

I support the application:

a) without qualification X

b) with qualification

- on technical grounds

- on level of financial support

I do not support the application

Name of Referee: LARS A HANSON

Signature: .....

Date: 18/9/02

Position: Professor

Institution: Clinical Immunology Göteborg University

May 2002

CURRICULUM VITAE

NAME	CURRENT POSITIONS	ADDRESS
Lars Åke Persson Born 1947-07-23 (Id 470723-1439)	Professor, International Public Health, Umeå University, Sweden (leave of absence since March 1, 1999) Director, Public Health Sciences Division, ICDDR,B: Centre for Health and Population Research, Dhaka, Bangladesh	Public Health Sciences Divison, ICDDR,B GPO Box 128, Mohakhali CA. Dhaka 1000, Bangladesh Phone +880 2 9885155 Fax +880 2 8826050 e-mail persson@icddrb.org

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Uppsala University, Sweden	MD	1973	Medicine
Sandöskolan, Sweden	Certificate	1972-73	Aid and disaster relief training
Swedish Board of Health and Welfare	Certificate	1973	Tropical/international medicine
Gävle Hospital and Västernorrlands landsting, Sweden	Internship	1973-74	Medicine, Surgery, General practice
Dept Paediatrics, Örnsköldsvik Hospital, Sweden	Residency	1974-76	Paediatrics
Dept Paediatrics, Umeå University, Sweden	Residency	1978-79	Paediatrics
Dept Child Psychiatry, Umeå University, Sweden	Residency	1979	Paediatrics/child psychiatry
Dept Infectious Diseases, Umeå University, Sweden	Residency	1979	Paediatrics/infectious diseases
Swedish Board of Health and Welfare	Specialist	1980	Paediatrics
Umeå University, Sweden	PhD	1984	Paediatrics/Paediatric Nutrition
Dept Paediatrics, Umeå University, Sweden	Docent	1990	Paediatrics
Umeå University, Sweden	Professor	1998	International Public Health

PROFESSIONAL EXPERIENCE

(Internship and residency, see above)

1976-1978 Medical Officer, Ndolage Hospital, Tanzania
1980-1983 Fellow, Social Medicine, Umeå University, Sweden
1983-1984 Fellow, Dept Paediatrics, Umeå University, Sweden
1984-1985 Medical Advisor, Institute for Protection of Children's Health, Hanoi, Vietnam
1985-1986 Fellow, Dept Paediatrics, Umeå University, Sweden
1986-1990 Senior lecturer/researcher in Paediatrics/Epidemiology, Umeå University, Sweden
1990-1997 Associate professor, Dept Epidemiology and Public Health, Umeå University, Sweden
1998- Professor in International Public Health, Umeå University, Sweden
1999- Director, Public Health Sciences Division, ICDDR,B, Dhaka, Bangladesh

LANGUAGES

Swedish - mother-tongue; English – fluent; Kiswahili – fluent; Spanish – fair; German – fair; French – fair

RESEARCH ADVISOR

Current research students

Title of project/planned thesis	Degree	Student	Planned year of defence
Anaemia and iron deficiency in women. Impact of iron supplementation during pregnancy in rural Bangladesh	PhD	Zia Hyder (co-advisor)	2002
Micronutrient status and functional outcomes in infancy. Intervention studies in Indonesia and Sweden.	PhD	Torbjörn Lind	2003
Trauma exposure, resilience factors and mental health of refugee children in Sweden	PhD	Stephen Goldin (co-advisor)	2003
Equity in child health in Vietnam	PhD	Dinh Phuong Hoa	2003

Completed theses

Title	Degree	Student	Year
On the Multifactorial Etiology of Celiac Disease. An Epidemiological Approach to the Swedish Epidemic	PhD	Anneli Ivarsson	2001
Utilisation of health services in a transitional society: studies in Vietnam 1991-1999	PhD	Ngo Van Toan (co-advisor)	2001
Infant mortality in transitional Nicaragua	PhD	Rodolfo Peña	1999
Adolescent pregnancies in Nicaragua. The importance of education.	PhD	Elmer Zelaya Bladon (co-advisor)	1999
Child health in Somalia. An epidemiological assessment in rural communities during a pre-war period.	PhD	Mariam M Ibrahim	1998
Utilisation of reproductive health services in Vietnam	Licentiate	Ngo Van Toan	1996
Teenage sexuality and reproduction in Nicaragua. Gender and social differences	Licentiate	Elmer Zelaya Bladon	1996
Social patterning of child health in Vietnam	Licentiate	Dinh Phuong Hoa	1996
Family planning and reproductive patter in rural Vietnam	Licentiate	Hoang Thi Hoa	1996
Risk factors for future cardio-vascular diseases. A longitudinal study from adolescence to adulthood	PhD	Erik Bergström	1995
Studies for health planning in rural Somalia. Community perceptions and epidemiological data.	Licentiate	Abdulaziz S Aden	1994
The causation of konzo. Studies on a paralytic disease in Africa	PhD	Thorkild Tylleskär (co-advisor)	1994
Community involvement in epidemiology and preventive work - the case of a Swedish community	PhD	Inger Brännström (co-advisor)	1993

RESEARCH PROJECTS

Project	Role in project	Funding agency	Year(s)
The Bangladesh arsenic calamity and reproduction: Does arsenic contamination of drinking water result in fetal wastage, intrauterine growth retardation, neonatal deaths and impaired cognitive development, and to what extent can nutrition interventions reduce the risk?	Principal investigator	USAID, SAREC	2002-
Poverty and health studies	Principal investigator	DfID	2001-
Arsenic in tube well water and health consequences	Principal investigator	Sida, WHO	2001-
Socioeconomic determinants of child survival during warfare and rapid social transition. Infant mortality in Bavi district, Vietnam, 1965-98 (Collaborative project with Department of Social Paediatrics, Institute for Protection of Children's Health, Hanoi)	Principal investigator	SAREC	1999-
Pilot studies of arsenic exposure through drinking water and health consequneces in Matlab, Bangladesh	Principal investigator	USAID	2000-
Combined interventions to promote maternal and infant health (Collaborative project between ICDDR,B, UNICEF, and Cornell University, USA)	Principal investigator	UNICEF	2000-
Studies of the public health consequences of violence against women in Bangladesh (Collaboration ICDDR,B, Naripokkho, Bangladesh and WHO)	Co-investigator	Asian Development Bank (ADB)	2000-
Development of a questionnaire instrument for evaluation of causes of adult female deaths and maternal mortality, and the evaluation of causes of death in a nation-wide survey in Bangladesh (Collaboration with Johns Hopkins	Principal investigator	USAID through Johns Hopkins	2000-

University)			
Iron and zinc deficiency during infancy - causes, functional outcomes and the effect of an intervention. A cohort study in central Java. (Collaboration with Gadjah Mada University and Dept Nutrition UC Davis)	Principal investigator	SAREC, MFR	1995-
Determinants of compliance with iron and zinc supplementation in infancy. A cohort study in Central Java	Principal investigator	SAREC	1997-
Vitamin A supplementation and immunisation in practice in Bangladesh. A cohort study of the equity and effectiveness in preventing under five mortality (Collaboration with Research and Evaluation Division, BRAC, Bangladesh)	Principal investigator	SAREC	1997-
Effectiveness of iron supplementation programmes in pregnancy. The impact of dose frequency on compliance, side effects and haematological outcome (Collaborative project with BRAC, Bangladesh and Dept Nutrition, UC Davis)	Co-investigator	SAREC	1996-
Exposure to trauma, resilience factors, and mental health of refugee children in Sweden (Collaboration with Dept Child Psychiatry, Umeå university)	Principal investigator	Swedish Council for Planning and Co-ordination of Research (FRN), and from Swedish Council for Social Research (SFR)	1994-
Swedish Multicentre study of the incidence and aetiology of coeliac disease	Co-investigator, member of the steering committee	Swedish council for forestry and agricultural research (SJFR), The Swedish Foundation for Health Care Sciences and Allergy Research (Vårdal), and "Front-line research funds" of the Västerbotten county council.	1991-2001
Swedish participation in the multi centre study "Euro Growth Study" regarding feeding, growth and micronutrient health of infants 0-3 years of age	Principal investigator	Umeå university research funds (Central component financed by European union)	1991-1998
Health systems research in Vietnam (Collaborative project with Ministry of Health, Vietnam, Medical Faculty, Hanoi, IHCAR, KI, Nordic School of Public Health, Göteborg, and Epidemiology, Umeå University, Sweden.	Co-principal investigator	SAREC	1991-1999
Reproductive and child health in Nicaragua (Collaborative project with the Municipality Health Services, the Autonomous Nicaraguan University, and the Movimiento Comunal, León, Nicaragua)	Principal investigator	SAREC	1990-1999
Risk indicators in adolescence for future cardio-vascular diseases, the Umeå Youth Study	Co-principal investigator	Swedish council for social research (SFR)	1988-1995
The epidemiology of Epidemic Spastic Paraparesis (Konzo) in Zaire (Collaborative project between Nutrition Institute in Kinshasa (CEPLANUT), ICH, Uppsala University, and Epidemilogy, Umeå University, Sweden)	Co-investigator	SAREC	1988-1994
Swedish Childhood Diabetes Study	Co-investigator	MFR	1986-1991
Epidemiology in the planning of Primary Health Care (Collaboration with Community health department, Medical Faculty, Somali National University, Mogadishu, Somalia).	Co-investigator, later principal investigator	SAREC	1982-1992
Swedish multicentre study on food habits and nutrient intake in childhood in relation to health and socio-	Co-investigator	Swedish Food Administration	1979-1986

economic conditions (Collaborative study with Sedish Food Administration and Uppsala University)			

TEACHING

- Co-principal investigator and co-ordinator of a Fogarty training grant (200,000 $ per year) to Cornell university, USA, and ICDDR,B, Bangladesh, for training in Maternal and Infant Nutrition 2001-2005
- Course organiser and teacher at international course in Health and Demographic Surveillance and Advanced Analysis of Longitudinal Data, in Matlab, Bangladesh (2001)
- Course organiser and teacher at International Training Course in Epidemiology for Public Health in Matlab and Dhaka, Bangladesh (2000)
- Teacher in Epidemiology at courses in Epidemiology and research methodology at ICDDR,B, Dhaka (1999-)
- Course co-organiser and teacher at 5 credit courses in nutritional epidemiology at Umeå University (1997-1998).
- Production of the text book "Epidemiology for Public Health" (by Lars Åke Persson and Stig Wall) based on the teaching experiences and international courses during the 1980s and 1990s. See publication list number 100.
- Course organiser and teacher in 5 credit course in public health, epidemiology and biostatistics as part of the introductory semester for biomedicine students at the medical faculty, Umeå University (1996-1998).
- Director of studies at the Department of Epidemiology and Public Health, Umeå University and development of the curriculum and core course content of the Masters' of Public Health program at Umeå University (1994-95).
- Course organiser and teacher at courses in Epidemiology, 10 credits, which is part of the post graduate program in Public Health at Umeå University (1991-present). This course as well as the entire Public Health program is given in English with course participants from many countries. Also organiser and teacher in Advanced Epidemiology (10 credits) from 1994 to 1998.
- Invited teacher in nutritional epidemiology at the ESPGAN summer school in Austria, 1995.
- Teacher in international health, nutrition and epidemiology at 10 credit courses in International Health at Umeå University. (1991-present).
- Teacher in international health and nutrition at courses at the Swedish Agricultural University. (1986-1996).
- Organiser and teacher in international health (2 credits) within a multidisciplinary course (10 credits) on "Conditions in low income countries" at Umeå University. (1989)
- Co-ordinator and teacher at yearly research training courses (summer school) in "Epidemiology and Field Research Methods" with participants from Africa, Asia and Latin America as well as European countries in Umeå. (1988-present). These courses are intensive courses of 2-3 weeks duration, including a lot of "hands-on" experience of epidemiology.
- Invited speaker at the SAREC supported research seminar "Infections of the gastrointestinal and respiratory tract" at the National Institute of Hygiene and Epidemiology, Hanoi, Vietnam. (1988).
- Co-ordinator and teacher in courses in "Epidemiology and Field Research Methodology" at the Olof Palme Institute in Hanoi, Vietnam (1986), at King Edward's Medical College in Lahore, Pakistan (1986), at the Medical Faculty in Mogadishu, Somalia (1987), in Luanda, Angola (1987), in Harare, Zimbabwe (1988) and in Matagalpa, Nicaragua (1988). Intensive courses of 1-2 weeks duration. The teaching methods developed have been evaluated and reported in the Bulletin of the World Health Organization (see publication list number 25). Course material developed in English and Spanish (see publication list number 88 and 94).
- Teacher and course organiser for the courses in paediatrics at Medical Faculty, Umeå University. (1985-1987). Responsible for three courses of three months duration each.
- Teacher/organiser of seminars, courses and weekly post-graduate training of paediatricians and nurses at the Olof Palme Institute for Protection of Children's Health, Hanoi, Vietnam and at various regional hospitals in Vietnam. (1984-85). Several hours of teaching each week. Development of course material, which was replicated in training activities on lower levels in the health care system.
- Teacher and co-organiser of a research training course supported by SAREC "Epidemiology in Primary Health Care" in Mogadishu, Somalia. (1984). Intensive course of one week's duration.
- Teacher in Social Medicine and Epidemiology for medical students at the Department of Social Medicine, Medical Faculty, Umeå University. (1980-83). Course organiser, a few weeks of teaching per semester.
- Teacher in International Health and International Paediatrics for medical students at the Medical Faculty, Umeå University. (1978-1995).
- Teacher in Paediatrics and Child Health Care at Ndolage Nurses' Training School, Ndolage Hospital, Tanzania. (1976-78).

ADVISORY COMMITTEES, EXPERT MISSIONS ETC.

- Associate Editor, Journal of Health, Population and Nutrition (2001-)
- Member, Research Evaluation Committee, ICDDR,B (1999-)
- Executive board member, International Society for Research on Human Milk and Lactation (1998-2001)
- Member of the quality assurance group at the Medical Faculty, Umeå University (1997-1999).
- Faculty opponent at the defence of the PhD thesis of Bo Burström, Karolinska Institutet, "Risk factors for measles mortality. Studies from Kenya and 19th century Stockholm" (1996).
- Representative of the Medical Faculty in the Equal Opportunity Committee of Umeå University (1996-1999).

- Member of the research training committee (Forskarutbildningskomittén) at the Medical Faculty, Umeå University (1996-1999)
- Member of the advisory board for research grant applications to Swedish Medical Society (Svenska Läkaresällskapet) (1996- 1999)
- Chairman of the advisory group for research grants from the Joint Committee of the Northern County Councils at Umeå University (1995)
- Co-ordinator of the program support by the Swedish Public Health Institute to Umeå University for research on Child and Adolescent Health (1993-1999)
- Advisor to SIDA in its support to Tanzania Food and Nutrition Centre, Dar es Salaam. (1993-1999)
- Member of the research ethics committee at the Medical Faculty, Umeå University (1993-1999)
- Member of the SAREC advisory board for research in health and nutrition (1990-1997)
- Member of the board of the Working group of paediatric epidemiology of the Swedish Paediatric Association (1990-1994)
- Faculty opponent at the defence of the PhD thesis of Redda Tekle-Haimanots "Epidemiology of neurological disorders in Ethiopia" at Umeå University (1990)
- Secretary and member of an evaluation team for the SAREC support to the Pakistani-Swedish research project "Breast feeding in a developing country" at King Edward Medical College, Lahore, Pakistan (1989)
- Member of a working group of the Swedish Board of Health Welfare regarding the "Biological Development of Swedish Children" (1988-1990)
- Temporary WHO Adviser (Epidemiology) regarding "Research and action for the promotion of oral health within primary health care" (1987-1988)
- Member of the Swedish Research Council's (Forskningsrådsnämndens) advisory group on methodology in dietary studies (1980-85)
- Member of the project group "Processing of epidemiological data in a developing country - development of a micro-computer system" (1982-84)
- Referee for a number of scientific journals, e.g. Acta Paediatrica, International Journal of Epidemiology, American Journal of Clinical Nutrition, Scandinavian Journal of Social Medicine, Scandinavian Journal of Public Health, Journal of Health, Population and Nutrition

ORIGINAL PUBLICATIONS

1. Persson LÅ, Samuelson G, Johansson E, Osland-Johansson T. Vad äter svenska spädbarn? Se till hela familjens matvanor. [What do Swedish infants eat. Look at the food habits of the whole family].Läkartidningen 1982;79:3813-3816.
2. Samuelson G, Osland-Johansson T, Persson LÅ. Kvinnans kostvanor och näringsintag under graviditet. Näringsforskning 1983;27:22-25.
3. Brändström A, Broström G, Persson LÅ. The Impact of Feeding Patterns on Infant Mortality in a Nineteenth Century Swedish Parish. Journal of Tropical Pediatrics 1984;30:154-159.
4. Persson LÅ. Nutrition and health in infancy and childhood. An epidemiological approach to the assessment of dietary habits, their determinants and implications. Thesis. Umeå University Medical Dissertations New Series No 119. Umeå University, Umeå 1984.
5. Bruce Å, Hagman U, Persson LÅ, Samuelson G, Sjölin S. Näringsintag hos svenska barn. Resultat från en multicenterstudie 1980-1981. [Dietary intake among Swedish children. Results from a multi-centre study]. Vår Föda 1984;36:Suppl 2.
6. Persson LÅ, Johansson E, Samuelson G. From Breastmilk to Family Food. Infant Feeding in Three Swedish Communities. Acta Paediatr Scand 1984;73:685-692.
7. Persson LÅ, Johansson E, Samuelson G. Dietary intake of weaned infants in a Swedish community. Human Nutrition:Applied Nutrition 1984;38A:247-254.
8. Persson LÅ, Stecksén-Blicks C, Holm AK. Nutrition and health in childhood: causal and quantitative interpretations of dental caries. Community Dent Oral Epidemiol 1984;12:390-7.
9. Persson LÅ. Dietary habits and health risks in Swedish children. Human Nutrition:Clinical Nutrition 1984;38C:287-297.
10. Persson LÅ, Carlgren G. Measuring Children's Diets: Evaluation of Dietary Assessment Techniques in Infancy and Childhood. International Journal of Epidemiology 1984;13:506-517.
11. Persson LÅ. Multivariate approaches to the analysis of breast-feeding habits. Bulletin of the World Health Organization 1985;63:1129-1136.
12. Persson LÅ. Infant feeding and growth - a longitudinal study in three Swedish communities. Annals of Human Biology 1985;12:41-52.
13. Persson LÅ, Holm AK, Arvidsson S, Samuelson G. Infant feeding and dental caries - a longitudinal study of Swedish children. Swed Dent J 1985;9:201-6.
14. Hagman U, Bruce Å, Persson LÅ, Samuelson G, Sjölin S. Food Habits and Nutrient Intake in Childhood in Relation to Health and Socio-economic Conditions. A Swedish Multicentre Study 1980-81. Acta Paediatr Scand 1986; Suppl 328.
15. Thu NX, Cung HB, Liem NT, Cuóng PT, Persson LÅ. Surgical treatment of congenital cystic dilation of the biliary tract. Acta Chir Scand 1986;152:669-674.
16. Persson LÅ, Samuelson G. Vikt, längd och könsmognad bör sättas i relation till barns blodtryck. Läkartidningen 1987;84:109-110.
17. Blom L, Lundmark K, Dahlquist G, Persson LÅ. Estimating Children's Eating Habits. Validity of a Questionnaire Measuring Food Frequency Compared to a 7-Day Record. Acta Paediatr Scand 1989;78:858-64.
18. Persson LÅ, Samuelson G, Sjölin S. Nutrition and health in Swedish children 1930-1980. Three nutrition surveys in a northern Swedish county. Acta Paediatr Scand 1989;78:865-72.
19. Owour Omondi L, Persson LÅ, Staugård F. Determinants for breast-feeding and bottle-feeding in Botswana. J Tropical Pediatrics 1990;36:28-33.
20. Aden AS, Brännström I, Mohamud KA, Persson LÅ, Wall S. The growth chart - a road to health chart? Maternal comprehension of the growth chart in two Somali villages. Paediatric and Preinatal Epidemiology 1990;4:340-350.
21. Dahlquist GG, Blom LG, Persson LÅ, Sandström AIM, Wall SGI. Dietary factors and the risk of developing insulin dependent diabetes in childhood. BMJ 1990;300:1302-1306.

22. Tylleskär T, Banea M, Bikangi N, Fresco L, Persson LÅ, Rosling H. Epidemiological evidence from Zaire for a dietary etiology of konzo, an upper motor neuron disease. Bull World Health Org 1991;69:581-589.

23. Ibrahim MM, Persson LÅ, Omar MM, Wall S. Breast-feeding and dietary habits of children in rural Somalia. Acta Paediatrica 1992;81:480-483.

24. Blom LG, Persson LÅ, Dahlquist GG. A high linear growth is associated with an increased risk for childhood diabetes. Diabetologia, 1992;35:528-533.

25. Persson LÅ, Wall S. Epidemiology teaching and the community perspective. World Health Forum 1992;14:37-41.

26. Bergström E, Hernell O, Persson LÅ. Dietary changes in Swedish adolescents. Acta Paediatrica 1993;82:472-480.

27. Persson LÅ, Aden AS, Ibrahim MM, Omar MH, WallS. Famine in Somalia. The Lancet 1993;341:1478.

28. Brännström I, Weinehall L, Persson LÅ, Wester PO, Wall S. Changing social patterns of risk factors for cardiovascular disease in a Swedish community intervention programme. Int J Epidemiol 1993;22:1026-1037.

29. Brännström I, Persson LÅ, Wall S. Towards a Framework for Outcome Assessment of Health Intervention: Conceptual and Methodological Considerations. European Journal of Public Health 1994;4:125-130.

30. Ibrahim MM, Aden AS, Omar MH, Wall S, Persson LÅ. Diarrhoea among children in rural Somalia. Maternal perceptions, management and mortality.Annals of Tropical Paediatrics. 1994;14:215-222.

31. Brännström I, Persson LÅ, Wall S. Gender and social patterning of health - The Norsjö cardiovascular preventive program in northern Sweden 1985-1990. Scand J Prim Health Care 1994;12:155-61.

32. Blomquist H K:son, Jonsbo F, Serenius F, Persson LÅ. Supplementary feeding in the maternity ward shortens the duration of breast feeding. Acta Paediatrics 1994;83:1122-6.

33. Bergström E, Hernell O, Lönnerdal B, Persson LÅ. Sex differences in iron stores of adolescents. What is normal? J Pediatr Gastroenterol Nutr 1995;20:215-24.

34. Dewey KG, Peerson JM, Brown KH, Krebs NF, Michaelsen KF, Persson LA, Salmenpera L, Whitehead RG, Yeung DL. Growth of breastfed infants deviates from current reference data: A pooled analysis of U.S., Canadian and European datasets. Pediatrics 1995;96:495-503.

35. Tylleskär T, Banea M, Bikangi N, Nahimana G, Persson LÅ, Rosling H. Dietary determinants of a non-progressive spastic paraparesis (Konzo): a case-referent study in a high incidence area of Zaire. Int J Epidemiol 1995;24:949-56.

36. Bergström E, Hernell O, Persson LÅ, Vessby B. Serum lipids in adolescents are related to family history, infant feeding and physical growth. Atherosclerosis 1995;117:1-13.

37. Hoa DP, Thanh HT, Höjer B, Persson LÅ. Young child feeding in a rural area in the Red River delta, Vietnam. Acta Paediatrica 1995;84:1045-9.

38. Bergström E, Hernell O, Persson LÅ. Insulin resistance syndrome in adolescents. Metabolism 1996;45:908-914.

39. Toan NV, Hoa HT, Trong PV, Höjer B, Persson LÅ, Sundström K. Utilisation of reproductive health services in rural Vietnam - equal chances to plan and protect pregnancies? J Epidemiol Comm Health 1996;50:451-455.

40. Hoa HT, Toan VN, Johansson A, Höjer B, Hoa VT, Persson LÅ. Child spacing and two-child policy in practice in rural Vietnam. BMJ 1996;313:1113-6.

41. Hoa DP, Thanh HT, Hoa VT, Höjer B, Persson LÅ. Maternal factors influencing the occurrence of low birth weight in northern Vietnam. Ann Trop Pediatr 1996;16:327-33.

42. Ibrahim MM, Omar HM, Persson LÅ, Wall S. Child mortality in a collapsing African society. Bull World Health Organ 1996;74:547-552.

43. Zelaya E, Peña R, García J, Bergluñd S, Persson LÅ, Liljestrand J. Contraceptive patterns among women and men in León, Nicaragua. Contraception 1996;54:359-365.

44. Bergström E, Hernell O, Persson LÅ. Cardiovascular risk indicators cluster in girls from families of low socio-economic status. Acta Paediatrica 1996;85:1083-90.

45. Toan NV, Hoa HT, Thach NT, Höjer B, Persson LÅ. Utilization of reproductive health services in a mountainous area in Vietnam. Southeast Asian Journal of Tropical Medicine and Public Health 1996;27:325-32.

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Budget for MINIMat – Immune functionsin the next pregnancy

Designation	Pay-Level	# of post	Effort	Year-1			
				Rate	PM	Amount	Sub-total
Laboratory Officer	GS-5	1	100%	323	5	1,615	
Laboratory Technician	GS-3	1	100%	197	5	985	
							2,600
Travel and Transportation:							
Local travel, in/between Dhaka-Matlab							**250**
Supplies & Reagent:							
Antibodies and conjugates for immunostaining of placental tissue						3,000	
Elisa kits for measuring lactoferrin, IL-7, IgA & leptin in breast milk						10,000	
Disposable supplies						3,000	**16,000**
Total Operating Cost							**18,850**
Indirect Cost @ 32%							**6,032**
Total Project Cost							**24,882**

18/5/06

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Nutritional Solutions to Promote Optimal Maternal Health, Infant Growth, Pregnancy Outcome and Children's Mental Health

লিখিত সম্মতি পত্র

গর্ভকালীন অবস্থায় আমাদের গবেষনা কাজে অংশ গ্রহনের জন্য ধন্যবাদ । আমরা আপনাকে বাচ্চা জন্মের পরও আমাদের গবেষনা কাজে অংশ গ্রহনের জন্য অনুরোধ করছি। আপনার নিশ্চয়ই এই গবেষনা কাজ কেন করছি সে সম্পর্কে মনে আছে, তারপরেও আপনার সুবিধার জন্য এ সম্পর্কে কিছু তথ্য আমি আবার বলছি। গর্ভাবস্থায় মায়ের ভাল পুষ্টি এবং সংক্রামক রোগের চিকিৎসা মা ও তার শিশুর সুস্বাস্থ্য এবং মঙ্গলের জন্য খুবই গুরুত্বপূর্ণ । গর্ভাবস্থায় মায়ের অপুষ্টি এবং সংক্রামক রোগ বাংলাদেশে খুবই সাধারণ একটি ঘটনা যা মতলবের বেলায়ও প্রযোজ্য । এর ফলে মায়েদের শক্তি, আমিষ, ভিটামিন ও খনিজ পদার্থের অভাব হয়। এই কারণে মা ও শিশুদের অনেক অসুস্থতা এবং মৃত্যুর মুখোমুখি হতে হয়।

আই সি ডি ডি আর, বি, বাংলাদেশ সরকার, ইউনিসেফ এবং যুক্তরাষ্ট্র ও ইউরোপের সহযোগী বিশ্ববিদ্যালয় এর সহযোগিতায় মা ও শিশুর পুষ্টি অবস্থার উন্নতি করার জন্য একটি গবেষণা প্রকল্প হাতে নিয়েছে । আপনি গর্ভবস্থায় এই গবেষনায় অংশগ্রহন করেছেন - যেখানে পুষ্টি খাদ্য, ভিটামিন ও মিনারেল সমৃদ্ধ বড়ি, যোনীর সংক্রমন এবং বুকের দুধ খাওয়ানোর উপর বেশী গুরুত্ব দেয়া হয়েছে। 'পুষ্টি' খাদ্য কার্যক্রম, আপনার বাচ্চা জন্ম গ্রহনের পরও চলবে; আরও কয়েক মাস খেতে পারবেন এমন পরিমান ভিটামিন ও মিনারেল সমৃদ্ধ বড়ি আপনাকে দেয়া হয়েছে; এবং বুকের দুধ খাওয়ানোর উপর পরামর্শ অথবা আপনার বা শিশুর স্বাস্থ্য বিষয়ে পরামর্শ আরও দেয়া হবে। আমরা এখন গবেষনা করে দেখতে চাই, গর্ভবস্থায় আমাদের এই কার্যক্রম আপনার ও আপনার শিশুর দৈহিক ও মানসিক গঠনে কতদুর পর্যন্ত সহায়তা করছে।

[সাব সেন্টারে সন্তান প্রসবের ক্ষেত্রে: আমরা দুই টিউব (শিশি) রক্ত নাড়ী থেকে সংগ্রহ করব (আপনার অথবা আপনার শিশু শরীর থেকে না) এবং আমরা ফুল (প্লাসেন্টা) থেকে ছোট একটি অংশ সংগ্রহ করব, এবং সেটি কেমন আছে তা পরীক্ষা করে দেখব। আগামী এক বৎসরে আমরা ৩ বার আপনার শিশুর শিরা থেকে আবার ৩ মি.লি. (প্রায় আধা চা চামচের সমান) রক্ত টিউবে (শিশি) সংগ্রহ করব এবং পরীক্ষা করে দেখব যে, গর্ভাবস্থায় আপনি যে পুষ্টি খাদ্য ও ভিটামিন ও মিনারেল সমৃদ্ধ বড়ি খেয়েছেন তার কতটা প্রভাব আপনার শিশুর উপর ফেলেছে। এর মধ্যে একবার রক্ত পরীক্ষা করে আমরা আপনার শিশুর রক্তশূন্যতা আছে কিনা পরীক্ষা করব এবং আপনাকে জানাব। অন্যান্য পরীক্ষার রিপোর্ট আপনাকে জানানো হবে না তবে সে সকল পরীক্ষার ফল বৈজ্ঞানিক কাজে ব্যবহার করা জন্য আমরা আপনার অনুমতি চাচ্ছি।]

[সাব সেন্টারে বাচ্চা না হয়ে থাকলে – শিশুর ৭-১০ দিন বয়সে বাড়ীতে ভিসিটের সময়: আমরা আপনার বাচ্চার শিরা থেকে ছয় মাস বয়সে ৩ মি.লি. (প্রায় আধা চা চামচের সমান) রক্ত টিউবে (শিশি) সংগ্রহ করব এবং পরীক্ষা করে দেখব যে, গর্ভবস্থায় আপনি যে পুষ্টি খাদ্য ও ভিটামিন ও মিনারেল সমৃদ্ধ বড়ি খেয়েছেন তার কতটা প্রভাব আপনার শিশুর উপর ফেলেছে। এ সময় আমরা আপনার শিশুর রক্তশূন্যতা আছে কিনা তা পরীক্ষা করব এবং আপনাকে জানাব। অন্যান্য পরীক্ষার রিপোর্ট আপনাকে জানানো হবে না তবে সে সকল পরীক্ষার ফল বৈজ্ঞানিক কাজে ব্যবহার করার জন্য আমরা আপনার অনুমতি চাচ্ছি।]

আপনি হয়তো আলট্রাসোনোগ্রামের সাথে পরিচিত । আমরা আপনার শিশুকে ৩-৪ বার আলট্রাসোনোগ্রাম দিয়ে পরীক্ষা করব এবং দেখব গাইমাসের অবস্থা কেমন আছে (গাইমাস শরীরের একটি অংশ যা রোগ প্রতিরোধে সাহায্য করে)। এই পরীক্ষায় মাত্র কয়েক মিনিট লাগে এবং তা আপনার শিশুর কোন ক্ষতি করবেনা।

আমরা আপনার শিশুর ওজন ও শরীরের অন্যান্য মাপ বিভিন্ন সময় নেব এবং কয়েক বার আপনার ওজনও মাপব। আমরা আপনার ও আপনার শিশুর স্বাস্থ্য, খাদ্য ও মানসিক গঠনের উপর প্রশ্ন করব। এ সময় তিনবার চলায় ও খেলায় আমরা আপনার শিশুর বৃদ্ধি পরীক্ষা করব।

আমরা আপনার শিরা থেকে ৫.৫ মিলি (এক চা চামচের সমান) রক্ত সংগ্রহ করব - এবং আপনার রক্তে রক্তশুন্যতা আছে কি তা আপনাকে জানাব। অন্যান্য পরীক্ষার ফল আপনাকে জানানো হবে না তবে সে সকল পরীক্ষার ফল বৈজ্ঞানিক কাজে ব্যবহার করার জন্য আমরা আপনার অনুমতি চাচ্ছি। আমরা তিন বার আপনার বুকের দুধ সংগ্রহের অনুমতি চাচ্ছি – আপনার বুকের দুধ পরীক্ষা করে তার মধ্যে পুষ্টি খাদ্য এবং ভিটামিন ও মিনারেল ট্যাবলেটের কতটা প্রভাব পরেছে তা দেখব।

আমরা আপনাকে নিশ্চয়তা দিচ্ছি আপনার কাছ থেকে যে সকল তথ্য সংগ্রহ করা হবে তা গোপন রাখা হবে। এই গবেষণা কাজ সংক্রান্ত সকল কাগজপত্র আই সি ডি ডি আর, বি' র মতলব ও ঢাকা অফিসে নিরাপদে তালাবদ্ধ রাখা হবে। যারা এই গবেষণার সাথে জড়িত শুধুমাত্র তারাই কেবল এ সকল কাগজপত্র দেখতে পারবে। যে সকল কাগজ পত্র আই সি ডি ডি আর, বি' র বাইরে নেয়া হবে সেখানে আপনাদের কারও নাম থাকবে না।

এই কাজে আপনার অংশগ্রহণ সম্পূর্ণ স্বেচ্ছামূলক। কোন রকম দায়বদ্ধতা অথবা নিয়মিত স্বাস্থ্য সেবায় কোন পরিবর্তন ছাড়াই এই গবেষণা থেকে যে কোন সময়ে সরে আসার পূর্ণ স্বাধীনতা আপনার আছে । আপনি যদি এই গবেষণায় অংশগ্রহণ নাও করেন তবুও আপনি ও আপনার পরিবারের আই সি ডি ডি আর,বি থেকে স্বাস্থ্য সেবায় কোন প্রকার ত্রুটি হবে না - আপনি বরাবরের মতই আমাদের নিয়মিত সেবা এবং প্রয়োজনীয় সহযোগিতা ও চিকিৎসা পেয়ে যাবেন।

আপনি এই গবেষণা সংক্রান্ত যে কোন প্রশ্ন করতে পারেন এবং আমি আনন্দের সাথে তার জবাব দেব। আপনি যে কোন সমস্যা বা প্রশ্নের জন্য আপনার কাছের স্বাস্থ্যকর্মীর সাথে অথবা আই সি ডি ডি আর,বি মতলব হাসপাতালে অথবা ডাঃ লার্স অকে পারসনের সাথে এই ফোন নম্বরে যে কোন সময় যোগাযোগ করতে পারেনঃ ৯৮৮ ৫১৫৫ (ঢাকা)

- আপনার কি কোন প্রশ্ন আছে ? হ্যাঁ না
- আপনি কি এই গবেষণায় অংশগ্রহণে সম্মত আছেন ? হ্যাঁ না

স্বাক্ষীর স্বাক্ষর (প্যারামেডিক)

গর্ভবতী মহিলার স্বাক্ষর/টিপসই

তারিখ: ____/____/____

ICDDR,B: Centre for Health and Population Research
Combined Interventions to Promote Maternal and Infant Health: Effects Over a Pregnancy Cycle and on Children 0-24 Months

লিখিত সম্মতি পত্র

গর্ভকালীন অবস্থায় আমাদের গবেষনা কাজে অংশ গ্রহনের জন্য ধন্যবাদ। আমরা আপনাকে আপনার শিশু জন্মের পরও আমাদের গবেষনা কাজে অংশ গ্রহনের জন্য অনুরোধ করছি। আপনার নিশ্চয়ই এই গবেষনা কাজ কেন করছি সে সম্পর্কে মনে আছে, তারপরেও আপনার সুবিধার জন্য এ সম্পর্কে কিছু তথ্য আমি আবার বলছি। গর্ভাবস্থায় মায়ের ভাল পুষ্টি এবং সংক্রামক রোগের চিকিৎসা মা ও তার শিশুর সুস্বাস্থ্য এবং মঙ্গলের জন্য খুবই গুরুত্বপূর্ণ। গর্ভাবস্থায় মায়ের অপুষ্টি এবং সংক্রামক রোগ বাংলাদেশে খুবই সাধারণ একটি ঘটনা যা মতলবের বেলায়ও প্রযোজ্য। এর ফলে মায়েদের শক্তি, আমিষ, ভিটামিন ও খনিজ পদার্থের অভাব হয়। এই কারনে মা ও শিশুরদের অনেক অসুস্থতা এবং মৃত্যুর মুখোমুখি হতে হয়।

আই.সি.ডি.ডি.আর.বি, বাংলাদেশ সরকার, ইউনিসেফ এবং যুক্তরাষ্ট্র ও ইউরোপের সহযোগী বিশ্ববিদ্যালয় এর সহযোগিতায় মা ও শিশুর পুষ্টি অবস্থার উন্নতি করার জন্য একটি গবেষণা প্রকল্প হাতে নিয়েছে। আপনি গর্ভাবস্থায় এই গবেষনায় অংশগ্রহন করেছেন - যেখানে পুষ্টি খাদ্য ভিটামিন ও খনিজ সমৃদ্ধ বড়ি, যোনীর সংক্রমন এবং বুকের দুধ খাওয়ানোর উপর বেশী গুরুত্ব দেয়া হয়েছে। 'পুষ্টি' খাদ্য কার্যক্রম, আপনার শিশু জন্ম গ্রহনের পরও চলবে; আরও কয়েক মাস খেতে পারবেন এমন পরিমান ভিটামিন ও খনিজ সমৃদ্ধ বড়ি আপনাকে দেয়া হয়েছে; এবং বুকের দুধ খাওয়ানোর উপর পরামর্শ অথবা আপনার বা শিশুর স্বাস্থ্য বিষয়ে পরামর্শ আরও দেয়া হবে। আমরা এখন গবেষনা করে দেখতে চাই, গর্ভাবস্থায় আমাদের এই কার্যক্রম আপনার ও আপনার সেই গর্ভাবস্থার শিশুর এবং পরবর্তীতে আপনার আবারও যদি গর্ভাবস্থা হয় তাহলে সেই শিশুর দৈহিক ও মানসিক গঠনে কতদূর সহায়তা করছে।

[*সাব সেন্টারে সন্তান প্রসবের ক্ষেত্রেঃ* আমরা রক্ত নাড়ী থেকে ৮.০ মিলি রক্ত সংগ্রহ করব (আপনার অথবা আপনার শিশুর শরীর থেকে না) এবং আমরা ফুল (প্লাসেন্টা) থেকে ছোট একটি অংশ সংগ্রহ করব এবং সেটি কেমন আছে তা পরীক্ষা করে দেখব। আগামী এক বৎসরে আমরা ৩ বার আপনার শিশুর শিরা থেকে প্রতিবারে আবার ৪ মি.লি. (প্রায় এক চা চামচের সমান) রক্ত সংগ্রহ করব এবং পরীক্ষা করে দেখব যে, গর্ভাবস্থায় আপনি যে পুষ্টি খাদ্য ও ভিটামিন ও খনিজ সমৃদ্ধ বড়ি খেয়েছেন তার কতটা প্রভাব আপনার শিশুর উপর ফেলেছে। এর মধ্যে একবার রক্ত পরীক্ষা করে আমরা আপনার শিশুর রক্তশুন্যতা আছে কিনা পরীক্ষা করব এবং আপনাকে জানাব। অন্যান্য পরীক্ষার রিপোর্ট আপনাকে জানানো হবে না তবে সে সকল পরীক্ষার ফল বৈজ্ঞানিক কাজে ব্যবহার করার জন্য আমরা আপনার অনুমতি চাচ্ছি।]

[*সাব সেন্টারে বাচ্চা না হয়ে থাকলেঃ* শিশুর ৭-১০ দিন বয়সে বাড়ীতে ভিজিটের সময় আমরা আপনার বাচ্চার শিরা থেকে ছয় মাস বয়সে ৪ মি.লি. (প্রায় এক চা চামচের সমান) রক্ত সংগ্রহ করব এবং পরীক্ষা করে দেখব যে, গর্ভাবস্থায় আপনি যে পুষ্টি খাদ্য ও ভিটামিন ও খনিজ সমৃদ্ধ বড়ি খেয়েছেন তার কতটা প্রভাব আপনার শিশুর উপর ফেলেছে। এ সময় আমরা আপনার শিশুর রক্তশূন্যতা আছে কিনা তা পরীক্ষা করব এবং আপনাকে জানাব। অন্যান্য পরীক্ষার রিপোর্ট আপনাকে জানানো হবে না তবে সে সকল পরীক্ষার ফল বৈজ্ঞানিক কাজে ব্যবহার করার জন্য আমরা আপনার অনুমতি চাচ্ছি।]

আপনি আলট্রাসোনোগ্রামের সাথে পরিচিত। আমরা আপনার শিশুকে ৩-৪ বার আলট্রাসোনোগ্রাম দিয়ে পরীক্ষা করব এবং দেখব থাইমাসের অবস্থা কেমন আছে (থাইমাস শিশুর বুকে অবস্থিত শরীরের একটি অংশ যা রোগ প্রতিরোধে সাহায্য করে)। এই পরীক্ষায় মাত্র কয়েক মিনিট লাগে এবং তা আপনার শিশুর কোন ক্ষতি করবেনা।

আমরা আপনার শিশুর ওজন ও শরীরের অন্যান্য মাপ বিভিন্ন সময় নেব এবং কয়েক বার আপনার ওজনও মাপব। আমরা আপনার ও আপনার শিশুর স্বাস্থ্য, খাদ্য ও মানসিক গঠনের উপর প্রশ্ন করব। এ সময় তিনবার চলায় ও খেলায় আমরা শিশুর বৃদ্ধি পরীক্ষা করব।

আমরা আপনার শিরা থেকে ৫.৫ মিলি (এক চা চামচের সমান) রক্ত সংগ্রহ করব এবং আপনার রক্তশুন্যতা আছে কি না তা আপনাকে জানাব। পরীক্ষা করে দেখব যে, গর্ভাবস্থায় আপনি যে পুষ্টি খাদ্য ও ভিটামিন ও খনিজ সমৃদ্ধ বড়ি খেয়েছেন তার কতটা প্রভাব আপনার উপর ফেলেছে। অন্যান্য পরীক্ষার ফল আপনাকে জানানো হবে না তবে সে সকল পরীক্ষার ফল বৈজ্ঞানিক কাজে ব্যবহার করার জন্য আমরা আপনার অনুমতি চাচ্ছি। আমরা তিনবার আপনার বুকের দুধ সংগ্রহের অনুমতি চাচ্ছি- আপনার বুকের দুধ পরীক্ষা করে তার মধ্যে পুষ্টি খাদ্য এবং ভিটামিন ও খনিজ বড়ির কতটা প্রভাব পড়েছে তা দেখব।

আমরা আপনাকে নিশ্চয়তা দিচ্ছি যে আপনার কাছে থেকে যে সকল তথ্য সংগ্রহ করা হবে তা গোপন রাখা হবে। এই গবেষনা কাজ সংক্রান্ত সকল কাগজপত্র আই.সি.ডি.ডি.আর.বির মতলব ও ঢাকা অফিসে নিরাপদে তালাবদ্ধ রাখা হবে। যারা এই গবেষণার সাথে জড়িত শুধুমাত্র তারা এবং আই.সি.ডি.ডি.আর.বির নীতি পর্যালোচনা কমিটি এ সকল কাগজপত্র দেখতে পারবে। যে সকল কাগজ পত্র আই.সি.ডি.ডি.আর.বির বাইরে নেয়া হবে সেখানে আপনাদের কারও নাম থাকবে না।

এই কাজে আপনার অংশগ্রহন সম্পূর্ন স্বেচ্ছামুলক। কোন রকম দায়বদ্ধতা অথবা নিয়মিত স্বাস্থ্য সেবায় কোন পরিবর্তন ছাড়াই এই গবেষণা থেকে যে কোন সময়ে আপনার সম্মতি প্রত্যাহার করার পূর্ণ স্বাধীনাতা আপনার আছে। আপনি যদি এই গবেষণায় অংশগ্রহন নাও করেন তবুও আপনি ও আপনার পরিবারের আই.সি.ডি.ডি.আর.বি থেকে স্বাস্থ্যসেবায় কোন প্রকার ত্রুটি হবে না-আপনি বরাবরের মতোই আমাদের নিয়মিত সেবা এবং প্রয়োজনীয় সহযোগিতা ও চিকিৎসা পেয়ে যাবেন।

আপনি এই গবেষণা সংক্রান্ত যে কোন প্রশ্ন করতে পারেন এবং আমি আনন্দের সাথে তার জবাব দেব। আপনি যে কোন সমস্যা বা প্রশ্নের জন্য আপনার কাছের স্বাস্থ্যকর্মীর সাথে অথবা আই.সি.ডি.ডি.আর.বির মতলব হাসপাতালে অথবা ডাঃ সামস্ এল আরেফিন এর সাথে এই ফোন নম্বরে যে কোন সময়ে যোগাযোগ করতে পারেনঃ ৮৮১০১১৫ (ঢাকা)

- আপনার কি কোন প্রশ্ন আছে? হ্যাঁ না
- আপনি কি এই গবেষণায় অংশগ্রহণে সম্মত আছেন? হ্যাঁ না

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স্বাক্ষীর স্বাক্ষর (প্যারামেডিক) গর্ভবতী মহিলার স্বাক্ষর/টিপসই

তারিখঃ _____/_____/_____

ICDDR,B: Centre for Health and Population Research
Combined Interventions to Promote Maternal and Infant Health: Effects Over a Pregnancy Cycle and on Children 0-24 Months

লিখিত সম্মতি পত্র

গর্ভকালীন অবস্থায় আমাদের গবেষনা কাজে অংশ গ্রহনের জন্য ধন্যবাদ। আমরা আপনাকে শিশু জন্মের পরও আমাদের গবেষনা কাজে অংশ গ্রহনের জন্য অনুরোধ করছি। আপনার নিশ্চয়ই এই গবেষনা কাজ কেন করছি সে সম্পর্কে মনে আছে, তারপরেও আপনার সুবিধার জন্য এ সম্পর্কে কিছু তথ্য আমি আবার বলছি। গর্ভাবস্থায় মায়ের ভাল পুষ্টি এবং সংক্রামক রোগের চিকিৎসা মা ও তার শিশুর সুস্বাস্থ্য এবং মঙ্গলের জন্য খুবই গুরুত্বপূর্ণ। গর্ভাবস্থায় মায়ের অপুষ্টি এবং সংক্রামক রোগ বাংলাদেশে খুবই সাধারণ একটি ঘটনা যা মতলবের বেলায়ও প্রযোজ্য। এর ফলে মায়েদের শক্তি, আমিষ, ভিটামিন ও খনিজ পদার্থের অভাব হয়। এই কারনে মা ও শিশুরদের অনেক অসুস্থতা এবং মৃত্যুর মুখোমুখি হতে হয়।

আই.সি.ডি.ডি.আর.বি, বাংলাদেশ সরকার, ইউনিসেফ এবং যুক্তরাষ্ট্র ও ইউরোপের সহযোগী বিশ্ববিদ্যালয় এর সহযোগিতায় মা ও শিশুর পুষ্টি অবস্থার উন্নতি করার জন্য একটি গবেষণা প্রকল্প হাতে নিয়েছে। আপনি গর্ভাবস্থায় এই গবেষনায় অংশগ্রহন করেছেন - যেখানে পুষ্টি খাদ্য ভিটামিন ও খনিজ সমৃদ্ধ বড়ি, যোনীর সংক্রমন এবং বুকের দুধ খাওয়ানোর উপর বেশী গুরুত্ব দেয়া হয়েছে। 'পুষ্টি' খাদ্য কার্যক্রম, আপনার শিশু জন্ম গ্রহনের পরও চলবে; আরও কয়েক মাস খেতে পারবেন এমন পরিমান ভিটামিন ও খনিজ সমৃদ্ধ বড়ি আপনাকে দেয়া হয়েছে; এবং বুকের দুধ খাওয়ানোর উপর পরামর্শ অথবা আপনার বা শিশুর স্বাস্থ্য বিষয়ে পরামর্শ আরও দেয়া হবে। আমরা এখন গবেষনা করে দেখতে চাই, গর্ভাবস্থায় আমাদের এই কার্যক্রম আপনার ও আপনার বর্তমান গর্ভাবস্থার শিশুর এবং পরবর্তীতে আপনার আবারও যদি গর্ভাবস্থা হয় তাহলে সেই শিশুর দৈহিক ও মানসিক গঠনে কতদূর পর্যন্ত সহায়তা করছে।

[*সাব সেন্টারে সন্তান প্রসবের ক্ষেত্রেঃ* আমরা ~~দুই টিউব~~ (শিশি) রক্ত নাড়ী (৮.০ মিলি) থেকে সংগ্রহ করব (আপনার অথবা আপনার শিশুর শরীর থেকে না) এবং আমরা ফুল (প্লাসেন্টা) থেকে ছোট একটি অংশ সংগ্রহ করব এবং সেটি কেমন আছে তা পরীক্ষা করে দেখব। আগামী এক বৎসরে আমরা ৩ বার আপনার শিশুর শিরা থেকে প্রতিবারে আবার ৪ মি.লি. (প্রায় এক চা চামচের সমান) রক্ত টিউবে (শিশি) সংগ্রহ করব এবং পরীক্ষা করে দেখব যে, গর্ভাবস্থায় আপনি যে পুষ্টি খাদ্য ও ভিটামিন ও খনিজ সমৃদ্ধ বড়ি খেয়েছেন তার কতটা প্রভাব আপনার শিশুর উপর ফেলেছে। এর মধ্যে একবার রক্ত পরীক্ষা করে আমরা আপনার শিশুর রক্তশুন্যতা আছে কিনা পরীক্ষা করব এবং আপনাকে জানাব। অন্যান্য পরীক্ষার রিপোর্ট আপনাকে জানানো হবে না তবে সে সকল পরীক্ষার ফল বৈজ্ঞানিক কাজে ব্যবহার করার জন্য আমরা আপনার অনুমতি চাচ্ছি।]

[*সাব সেন্টারে বাচ্চা না হয়ে থাকলেঃ* শিশুর ৭-১০ দিন বয়সে বাড়ীতে ভিজিটের সময় আমরা আপনার বাচ্চার শিরা থেকে ছয় মাস বয়সে ৪ মি.লি. (প্রায় এক চা চামচের সমান) রক্ত সংগ্রহ করব এবং পরীক্ষা করে দেখব যে, গর্ভাবস্থায় আপনি যে পুষ্টি খাদ্য ও ভিটামিন ও খনিজ সমৃদ্ধ বড়ি খেয়েছেন তার কতটা প্রভাব আপনার শিশুর উপর ফেলেছে। এ সময় আমরা আপনার শিশুর রক্তশূন্যতা আছে কিনা তা পরীক্ষা করব এবং আপনাকে জানাব। অন্যান্য পরীক্ষার রিপোর্ট আপনাকে জানানো হবে না তবে সে সকল পরীক্ষার ফল বৈজ্ঞানিক কাজে ব্যবহার করার জন্য আমরা আপনার অনুমতি চাচ্ছি।]

আপনি আলট্রাসোনোগ্রামের সাথে পরিচিত। আমরা আপনার শিশুকে ৩-৪ বার আলট্রাসোনোগ্রাম দিয়ে পরীক্ষা করব এবং দেখব থাইমাসের অবস্থা কেমন আছে (থাইমাস শিশুর বুকে অবস্থিত শরীরের একটি অংশ যা রোগ প্রতিরোধে সাহায্য করে)। এই পরীক্ষায় মাত্র কয়েক মিনিট লাগে এবং তা আপনার শিশুর কোন ক্ষতি করবেনা।

আমরা আপনার শিশুর ওজন ও শরীরের অন্যান্য মাপ বিভিন্ন সময় নেব এবং কয়েক বার আপনার ওজনও মাপব। আমরা আপনার ও আপনার শিশুর স্বাস্থ্য, খাদ্য ও মানসিক গঠনের উপর প্রশ্ন করব। এ সময় তিনবার চলায় ও খেলায় আমরা শিশুর বৃদ্ধি পরীক্ষা করব।

আমরা আপনার শিরা থেকে ৫.৫ মিলি (এক চা চামচের সমান) রক্ত সংগ্রহ করব এবং আপনার রক্তে রক্তশুন্যতা আছে কি না তা আপনাকে জানাব। পরীক্ষা করে দেখব যে, গর্ভাবস্থায় আপনি যে পুষ্টি খাদ্য ও ভিটামিন ও খনিজ সমৃদ্ধ বড়ি খেয়েছেন তার কতটা প্রভাব আপনার উপর ফেলেছে। অন্যান্য পরীক্ষার ফল আপনাকে জানানো হবে না তবে সে সকল পরীক্ষার ফল বৈজ্ঞানিক কাজে ব্যবহার করার জন্য আমরা আপনার অনুমতি চাচ্ছি। আমরা তিনবার আপনার বুকের দুধ সংগ্রহের অনুমতি চাচ্ছি- আপনার বুকের দুধ পরীক্ষা করে তার মধ্যে পুষ্টি খাদ্য এবং ভিটামিন ও খনিজ বড়ির কতটা প্রভাব পড়েছে তা দেখব।

আমরা আপনাকে নিশ্চয়তা দিচ্ছি আপনার কাছে থেকে যে সকল তথ্য সংগ্রহ করা হবে তা গোপন রাখা হবে। এই গবেষনা কাজ সংক্রান্ত সকল কাগজপত্র আই.সি.ডি.ডি.আর.বির মতলব ও ঢাকা অফিসে নিরাপদে তালাবদ্ধ রাখা হবে। যারা এই গবেষণার সাথে জড়িত শুধুমাত্র তারাই কেবল এ সকল কাগজপত্র দেখতে পারবে। যে সকল কাগজ পত্র আই.সি.ডি.ডি.আর.বির বাইরে নেয়া হবে সেখানে আপনাদের কারও নাম থাকবে না।

এই কাজে আপনার অংশগ্রহন সম্পূর্ন স্বেচ্ছামুলক। কোন রকম দায়বদ্ধতা অথবা নিয়মিত স্বাস্থ্য সেবায় কোন পরিবর্তন ছাড়াই এই গবেষণা থেকে যে কোন সময়ে আপনার সম্মতি প্রত্যাহার করার পূর্ণ স্বাধীনাতা আপনার আছে। আপনি যদি এই গবেষণায় অংশগ্রহন নাও করেন তবুও আপনি ও আপনার পরিবারের আই.সি.ডি.ডি.আর.বি থেকে স্বাস্থ্যসেবায় কোন প্রকার ত্রুটি হবে না-আপনি বরাবরের মতোই আমাদের নিয়মিত সেবা এবং প্রয়োজনীয় সহযোগিতা ও চিকিৎসা পেয়ে যাবেন।

আপনি এই গবেষণা সংক্রান্ত যে কোন প্রশ্ন করতে পারেন এবং আমি আনন্দের সাথে তার জবাব দেব। আপনি যে কোন সমস্যা বা প্রশ্নের জন্য আপনার কাছের স্বাস্থ্যকর্মীর সাথে অথবা আই.সি.ডি.ডি.আর.বির মতলব হাসপাতালে অথবা ডাঃ সামস্ এল আরেফিন এর সাথে এই ফোন নম্বরে যে কোন সময়ে যোগাযোগ করতে পারেনঃ ৮৮১০১১৫ (ঢাকা)

- আপনার কি কোন প্রশ্ন আছে? হ্যাঁ না
- আপনি কি এই গবেষণায় অংশগ্রহণে সম্মত আছেন? হ্যাঁ না

স্বাক্ষীর স্বাক্ষর (প্যারামেডিক)

গর্ভবতী মহিলার স্বাক্ষর/টিপসই

তারিখঃ _____/_____/_____

ICDDR,B: Centre for Health and Population Research
Combined Interventions to Promote Maternal and Infant Health: Effects Over a Pregnancy Cycle and on Children 0-24 Months

WRITTEN CONSENT FORM

Thank you for participating in the study during pregnancy. We would like to invite you to continue to participate in the study even after child birth. I am sure you remember why we do this study, but let me repeat some of the information for your benefit. Good maternal nutrition and treatment of infection during pregnancy are very important for the health and well being of the mother and her baby. Poor maternal nutrition and infection during pregnancy are very common in Bangladesh, as in Matlab, which results in lack of energy/protein, vitamins and minerals. Because of this, a lot of illness and deaths take place among mothers and their babies.

ICDDR,B in collaboration with the Government of Bangladesh, UNICEF and collaborating universities in the United States and Europe is undertaking a study to improve maternal and infant nutrition status. You have participated in this during pregnancy, and it has focused the ongoing feeding program, tablets with vitamins and minerals, investigation regarding vaginal infection and advice regarding breast feeding. The "Pushti" program continues also after birth, you have received tablets with vitamins and minerals to take for some more months, and you will continue to receive either counseling to help you with breast-feeding of your baby or health education on care for yourself and the baby. We are now interested to study to what extent these interventions are benefiting your health and your child's health and further development.

[*Only when delivering at sub-centre*: We will collect two tubes of blood (8.0 ml) from the cord (not from you or your child) and we will also take a small piece of the placenta in order to examine health conditions in the placenta. We will also take 4 ml of blood in a tube from your child's veins at three different occasions during the first years in order to examine the effects of the food supplementation and the macronutrient tablets you received during pregnancy. We will examine the haemoglobin concentration on one of these occasions and inform you about the result. Other results will not be reported back, and we ask for your permission to use it for scientific purposes.]

[*Only when not delivering at sub-centre, during the 7-10 day home visit:* We will also take 4 ml of blood in a tube from your child's veins at 6 months in order to examine the effects of the food supplementation and the micronutrient tablets you received during pregnancy. We will examine the haemoglobin concentration and inform you about the result. Other results will not be reported back, and we ask for your permission to use it for scientific purposes.

You are familiar with ultrasound examination. We will examine your child with ultrasound on 3-4 occasions, and see how thymus, an organ that is involved in the defence against infections, is developing. This examination takes a few minutes and is not causing any harm for your child.

We will continue to measure weight and other body measurements on your child and also, for a few times, even your weight. We will also ask questions about your health and your child's health, feeding and development. On three occasions during the first years we will observe how your child advances in movements and in play.

We will also collect 5.5 ml of blood (about a teaspoonful) from your veins. We will test this blood for anaemia, and tell the result. We will also examine the blood for effects of the food supplementation and the macronutrient tablets you receive during pregnancy. Other results will not be told, and we ask for your permission to use it for scientific purposes. We will also ask you to get a portion of breast milk on three occasions, for analysis of effects of the food and micronutrient supplementation.

We assure you that we shall maintain the confidentiality about the information we collect from you. All records from this study at the Matlab Diarrhoea Hospital or the Dhaka offices of ICDDR,B will be kept private and in a locked location. Only people doing the study will be able to look at them. Any study records that are taken from ICDDR,B will not have any of the names of who took part in the study.

Your participation is absolutely voluntary. You are at liberty to withdraw from the study at any time during the study without any penalty or change in the routine care you or your child receives. If you decide not to take part in these parts of the study, it will not change the care you, your child or your family receives from ICDDR,B in any way. You will still receive our routine care and necessary support and treatment.

You may ask any questions regarding the study and I shall be happy to answer them for you. If you have any problems or questions you can contact your home health care worker, or contact Matlab Hospital of ICDDR,B or Dr. Shams El Arifeen at the following phone number at any time: 8810115 (Dhaka).

- Do you have any questions? Yes No
- Do you agree to participate in this study? Yes No

Signature of the witness
(Paramedic) Date: _____

Signature/thumb impression of pregnant woman

International Centre for Diarrhoeal Disease Research, Bangladesh
CENTRE FOR HEALTH & POPULATION RESEARCH
Mail : ICDDR,B, GPO Box 128, Dhaka-1000, Bangladesh
Phone : 880-2-8811751-60, Fax : 880-2-8823116, 8812530
Web : http://www.icddrb.org

Memorandum

7 May 2006

To : Dr. Shams El Arifeen
Principal Investigator of research protocol # 2002-031
Public Health Sciences Division (PHSD)

From: Prof. Alejandro Cravioto
Chairman
Research Review Committee (RRC)

Sub : Proposal for modification of research protocol # 2002-031

Thank you submitting the proposal for modifications of your research protocol # 2002-031 titled "Combined interventions to promote maternal and infant health: Effects over a pregnancy cycle and on children 0-24 months" for consideration of the RRC and presenting the proposal before the RRC in its meeting held on May 4, 2006. This is to inform you that after review and discussion, the Committee made following observations on the proposal:

a) Though the addendum proposal is based upon preliminary findings, providing those findings would enable to assess the strength of association.

b) Expressions of which cytokines would be sought from the placental tissues?

c) Budgetary provisions have not been attached to the addendum proposal, though additional costs would be involved.

d) Bangla version of the consent form should be submitted for review by the Committee.

You are advised to modify the proposal addressing above issues and to submit its modified version for consideration of the RRC Chair.

Thank you once again.

Copy: Director, PHSD