PBHSD 2002

International Centre for Diarrhoeal Disease Research, Bangladesh
CENTRE FOR HEALTH AND POPULATION RESEARCH
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Cable : Cholera Dhaka

Memorandum

20 November 2002

To : Professor Lars Åke Persson
Principal Investigator of protocol # 2002-029; and
Associate Director, Public Health Sciences Division

From: Professor Mahmudur Rahman
Chairman, Ethical Review Committee (ERC)

Sub : **Approval of protocol # 2002-029**

Thank you for your memo dated 20th November 2002 with the modified version of your protocol # 2002-029 entitled "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 intervention reduce risk?" The modified version of the protocol is hereby approved upon your satisfactory addressing of the issues raised by the ERC in its meeting held on 13th November 2002.

You shall conduct the study in accordance with the ERC-approved protocol; and shall be responsible for protecting the rights and welfare of the subjects and compliance with the applicable provisions of ERC Guidelines. You shall also submit report(s) as required under ERC Guidelines. Relevant excerpt of ERC Guidelines and 'Annual/Completion Report for Research Protocol involving Human Subjects' are attached for your information and guidance.

Thank you and I wish you all success in running the above-mentioned study.

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Memorandum

To: Professor Mahmudur Rahman
Chairperson, ERC

From: Professor Lars Ake Persson
Associate Director, Public Health Sciences Division

Date: 20 November 2002

Subject: **Protocol # 2002-029**

Thanks for your observations regarding Item # 4th on the face sheet and on one word in the Bangla consent form. This has now been corrected.

Thank you again.

Attachment 1 Revised Date: 20 Nov 2002

(FACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator: Lars Ake Persson

Application No. 2002-029

Title of Study: 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 intervention reduce the risk?

Trainee Investigator (if any): _____

Supporting Agency (if Non-ICDDR,B) USAID, SAREC

Project Status: _____

[x] New Study

[ ] Continuation with change

[ ] No change (do not fill out rest of the form)

Circle the appropriate answer to each of the following (If Not Applicable write NA)

1. Source of Population:
   - (a) Ill subjects — Yes (No)
   - (b) Non-ill subjects — (Yes) No
   - (c) Minor or persons under guardianship — (Yes) No

2. Does the Study Involve:
   - (a) Physical risk to the subjects — Yes (No)
   - (b) Social risk — Yes (No)
   - (c) Psychological risks to subjects — Yes (No)
   - (d) Discomfort to subjects — Yes (No)
   - (e) Invasion of privacy — Yes (No)
   - (f) Disclosure of information damaging to subject or others — Yes (No)

3. Does the Study Involve:
   - (a) Use of records (hospital, medical, death or other) — (Yes) No
   - (b) Use of fetal tissue or abortus — Yes (No)
   - (c) Use of organs or body fluids — (Yes) No

4. Are Subjects Clearly Informed About:
   - (a) Nature and purposes of the study — (Yes) No
   - (b) Procedures to be followed including alternatives used — (Yes) No
   - (c) Physical risk — (Yes) No
   - (d) Sensitive questions — (Yes) No
   - (e) Benefits to be derived — (Yes) No
   - (f) Right to refuse to participate or to withdraw from study — (Yes) No
   - (g) Confidential handling of data — (Yes) No
   - (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — (Yes) No

5. Will Signed Consent Form be Required:
   - (a) From subjects — (Yes) No
   - (b) From parents or guardian (if subjects are minor) — (Yes) No

6. Will precautions be taken to protect anonymity of subjects — (Yes) No

7. Check documents being submitted herewith to Committee:
   - ____ Umbrella proposal - Initially submit an with overview (all other requirements will be submitted with individual studies
   - X Protocol (Required)
   - X Abstract Summary (Required)
   - X Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw) (Required
   - X Informed consent form for subjects } com-bined
   - X Informed consent form for parent or guardian }
   - X Procedure for maintaining confidentiality
   - X Questionnaire or interview schedule*

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary

1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy
2. Example of the type of specific questions to be asked in the sensitive areas
3. An indication as to when the questionnaire will be presented to the Committee for review

We agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

Principal Investigator

Trainee

Revised version

Version: October 29, 2002

ICDDR,B: Centre for Health and Population Research

Combined Interventions to Promote Maternal and Infant health

লিখিত সম্মতি পত্র

এই গবেষণা কাজে অংশগ্রহনের জন্য আপনাকে ধন্যবাদ। আপনার নিশ্চয়ই এই গবেষণা কাজ সম্পর্কে সব কিছু মনে আছে, তারপরও আপনার সুবিধার জন্য কিছু তথ্য আমি আবার বলছি।

গর্ভকালীন অবস্থায় মায়ের যথাযথ পুষ্টি বিধান 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। এই অপুষ্টির 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, যুক্তরাষ্ট্রের কর্ণেল ইউনিভার্সিটি ও ইউনিসেফ এর সহযোগিতায় একটি গবেষণা প্রকল্প হাতে নিতে যাছে যা মা ও শিশুর পুষ্টি অবস্থার উন্নতি সাধন করবে। এই প্রকল্পের আওতায় চলতি 'পুষ্টি' কর্মসূচিকে সহযোগিতা করে আপনাদের মধ্যে কাউকে কাউকে শীঘ্র পুষ্টি কর্মসূচিতে অংশগ্রহণ করতে সাহায্য করা হবে, কেউ পূর্ণ বা অর্ধেক মাত্রায় আয়রণ ট্যাবলেট পাবে অথবা ১৫টি ভিটামিন ও খনিজ পদার্থ মিশ্রণ সম্বলিত একটি ট্যাবলেট পাবে (যার মধ্যে অর্ধেক মাত্রায় আয়রণ অন্তর্ভূক্ত) এর মাধ্যমে এই গবেষণাটি চলতি 'পুষ্টি' কর্মসূচিকে সহযোগিতা করবে। ইউনিসেফ ভিটামিন এবং খনিজের এই সংমিশ্রণটি গর্ভবতী মহিলাদের জন্য বিশেষ ভাবে তৈরী করেছে । এই ট্যাবলেটগুলো আপনাদেরকে বোতলে ভরে দেয়া হবে যা আপনারা বাসায় নিয়ে যেতে পারবেন। কে কোন ধরণের ট্যাবলেট পাবে তা লটারীতে নির্ধারণ করা হবে। শিশুর জন্মের পর আমরা আপনাকে শিশুকে বুকের দুধ খাওয়ানোর ওপর পরামর্শ দেব অথবা শিশুর যত্নের বিষয়ে স্বাস্থ্য পরামর্শ প্রদান করব।

আপনি যদি সম্মত হন তবে আমরা আজ স্বাস্থ্য কেন্দ্রে আপনাকে শারীরিক পরীক্ষা সহ গর্ভকালীন সকল পরীক্ষা-নিরীক্ষা করব, এবং আলটাসনোগ্রামের মাধ্যমে আপনার গর্ভের ভেতরের শিশুকে পর্যবেক্ষণ করব। আমরা দুই বার আপনার শিরা থেকে ৫.৫ মি.লি. (প্রায় এক চা চামচের সমান) এবং একবার আঙ্গুলের মাথা থেকে রক্ত সংগ্রহ করব। এই রক্ত পরীক্ষা করে আমরা আপনার রক্তশূণ্যতা এবং অন্যান্য ভিটামিন ও খনিজ লবণের অবস্থা জানব। আপনি সম্মত হলে, আমরা আজ আপনার যোনীর উপরিভাগ থেকে পরীক্ষার জন্য সোয়াব সংগ্রহ করব এবং পরীক্ষা করে জানব যে যোনীর কোন সংক্রমন আছে কিনা যার ফলে সময়ের আগেই শিশুর জন্মদান ঘটে। আপনার যোনীর এই সংক্রমন পাওয়া গেলে এবং কোন অস্বাভাবিক স্রাব না থাকলে আপনাকে হয় মেট্রোনিডাজল ঔষধ দিয়ে সাতদিনের চিকিৎসা দেয়া হবে বা একই রকম দেখতে কিন্তু যার মধ্যে ঐ ঔষধ নাই তা দেয়া হবে। কেউ জানবে না কে কি পাবে - লটারীর মাধ্যমে তা নির্ধারণ করা হবে। আমরা গর্ভকালীন সময়ে অন্ততঃ আরো তিনবার এই ক্লিনিকে আসার জন্য আপনাকে অনুরোধ করব। আপনি যখন আবার আসবেন তখন আজকের সবকিছুই আমরা আবার করব। ছয়মাসের গর্ভাবস্থায় আর একবার যোনী থেকে সোয়াব সংগ্রহ করব - ঔষধ খাওয়ার পর আপনি কতটুকু ভাল হয়েছেন তা দেখার জন্য। প্রতিবার ক্লিনিকে নিয়মিত গর্ভকালীন পরীক্ষার জন্য যে প্রসাব আপনার কাছ থেকে নেয়া হবে আমরা তার কিছু অংশ সংগ্রহ করে রাখব এবং পরবর্তীতে আর্সেনিক আছে কিনা এই প্রসাব পরীক্ষা করে দেখা হবে।

আমরা আপনাকে নিশ্চয়তা দিচ্ছি যে 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 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 অংশগ্রহন সম্পূর্ণ স্বেচ্ছামূলক। কোন রকম দায়বদ্ধতা ছাড়াই এই গবেষণা থেকে যে কোন সময়ে সরে আসার পূর্ণ স্বাধীনতা আপনার আছে । আপনি যদি এই গবেষণায় অংশগ্রহন নাও করেন তবুও আপনি ও আপনার পরিবারের আই সি ডি ডি আর, বি থেকে কোন চিকিৎসার ত্রুটি হবে না। একবার এই গবেষণায় অংশগ্রহনে সম্মত হওয়ার পরও আপনি চাইলে যে কোন সময় এই গবেষণা থেকে আপনি নিজে কিংবা আপনার সন্তানের অংশগ্রহন প্রত্যাহার করে নিতে পারেন এবং তাতেও নিয়মিত যে সেবা আপনি কিংবা আপনার সন্তান পেয়ে আসছেন তার কোন পরিবর্তন হবে না । আপনি বরাবরের মতই আমাদের নিয়মিত সেবা এবং প্রয়োজনীয় সহযোগিতা ও চিকিৎসা পেয়ে যাবেন।

আপনি এই গবেষণা সংক্রান্ত যে কোন প্রশ্ন আমাদের করতে পারেন এবং আমরা আনন্দের সাথে তার জবাব দেব। আপনি যে কোন সমস্যা বা প্রশ্নের জন্য আপনার পারিবারিক স্বাস্থ্যকর্মীর সাথে যোগাযোগ করতে পারবেন।

এই গবেষণা সম্পর্কে আপনার কোন প্রশ্ন থাকলে আমি সানন্দে তার উত্তর দেব। আপনি আই সি ডি ডি আর, বি মতলব হাসপাতালেও যোগাযোগ করতে পারেন অথবা ডাঃ লার্স অকে পারসনের সাথে নিচের ফোন নম্বরে যে কোন সময় যোগাযোগ করতে পারেনঃ ৯৮৮ ৫১৫৫ (ঢাকা)

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

স্বাক্ষীর স্বাক্ষও (প্যারামেডিক)

গর্ভবতী মায়ের স্বাক্ষর/টিপসই

তারিখ ঃ

International Centre for Diarrhoeal Disease Research, Bangladesh
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Cable : Cholera Dhaka

Memorandum

17 November 2002

To : Professor Lars Åke Persson
Principal Investigator of protocol # 2002-029; and
Associate Director, Public Health Sciences Division

From : Professor Mahmudur Rahman
Chairman, Ethical Review Committee (ERC)

Sub : **Protocol # 2002-029**

Thank you for your protocol # 2002-029 entitled "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 intervention reduce risk?", which the ERC considered in its meeting held on 13th November 2002. After review and discussion, the following observations were made on the protocol:

a) On the ERC Face Sheet, item # 4(h) should be marked 'yes'.

b) On the Bangla consent form, the word 'সাভাবিত' should be replaced by the word 'পূর্ন'.

You are, therefore, advised to modify the protocol incorporating the above observations and submit the modified version of the protocol for consideration of the Chair.

Thank you.

Attachment I

Date: 03/11/2002

(FACE SHEET) **ETHICAL REVIEW COMMITTEE, ICDDR,B.**

Principal Investigator: Professor Lars Ake Persson

Application No. 2002-029

Title of Study: 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, ...intervention reduce the risk?

Trainee Investigator (if any): _____

Supporting Agency (if Non-ICDDR,B) USAID, SAREC

Project Status: _____

[X] New Study

[ ] Continuation with change

[ ] No change (do not fill out rest of the form)

Circle the appropriate answer to each of the following (If Not Applicable write NA)

1. Source of Population:
   - (a) Ill subjects — Yes (No)
   - (b) Non-ill subjects — (Yes) No
   - (c) Minor or persons under guardianship — (Yes) No

2. Does the Study Involve:
   - (a) Physical risk to the subjects — Yes (No)
   - (b) Social risk — Yes (No)
   - (c) Psychological risks to subjects — Yes (No)
   - (d) Discomfort to subjects — Yes (No)
   - (e) Invasion of privacy — Yes (No)
   - (f) Disclosure of information damaging to subject or others — Yes (No)

3. Does the Study Involve:
   - (a) Use of records (hospital, medical, death or other) — (Yes) No
   - (b) Use of fetal tissue or abortus — Yes (No)
   - (c) Use of organs or body fluids — (Yes) No

4. Are Subjects Clearly Informed About:
   - (a) Nature and purposes of the study — (Yes) No
   - (b) Procedures to be followed including alternatives used — (Yes) No
   - (c) Physical risk — (Yes) No
   - (d) Sensitive questions — (Yes) No
   - (e) Benefits to be derived — (Yes) No
   - (f) Right to refuse to participate or to withdraw from study — (Yes) No
   - (g) Confidential handling of data — (Yes) No
   - (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — Yes (No)

5. Will Signed Consent Form be Required:
   - (a) From subjects — (Yes) No
   - (b) From parents or guardian (if subjects are minor) — (Yes) No

6. Will precautions be taken to protect anonymity of subjects — (Yes) No

7. Check documents being submitted herewith to Committee:
   - ___ Umbrella proposal - Initially submit an with overview (all other requirements will be submitted with individual studies
   - X Protocol (Required)
   - X Abstract Summary (Required)
   - X Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw) (Required
   - X Informed consent form for subjects } combined
   - X Informed consent form for parent or guardian } combined
   - X Procedure for maintaining confidentiality
   - X Questionnaire or interview schedule*

   * If the final instrument is not completed prior to review, the following information should be included in the abstract summary
   1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy
   2. Example of the type of specific questions to be asked in the sensitive areas
   3. An indication as to when the questionnaire will be presented to the Committee for review

We agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

_____
Principal Investigator

_____
Trainee

Summary for ethical review, 2002-029

This project will generate new and highly needed knowledge on the associations between arsenic exposures and negative reproductive outcomes, such as miscarriages, stillbirths, and neonatal mortality for use in the national and international risk assessments. Further, the studies will provide answer to the question if the arsenic contamination of the drinking water is causing foetal growth restriction and impaired infant growth and development. Such information is much needed in the discussion and forecasting of the arsenic-related health consequences in Bangladesh. The results will further give a solid platform for evaluation of needs for arsenic mitigation interventions.

1. This study is nested into a trial, where pregnant women are invited to participate in food and micronutrient supplementation, as well as blood sampling for micronutrients, and urine sampling for routine antenatal control (RRC 2000-025 and the follow-up of that protocol, 2002-031). A portion of the antenatal routine urine sample is stored in freezers for later arsenic analyses. We have earlier obtained permission from the ERC to store these urine samples for this forthcoming analysis (addendum to protocol 2000-025*). Thus, the current protocol does not imply any additional collection of information or samples, but describes the use of the urine samples and analysis in relation to outcomes described in protocol 2002-025 and 2002-031.*
2. This protocol only implies analyses of urine samples already obtained as part of protocol 2000-025, and statistical analyses in relation to the outcomes assessed in protocol 2000-025 and its follow-up 2002-031. Thus, it does not imply any risks to the participants.
3. There are no potential risks.
4. Confidentiality of information will be strictly followed, and access to data forms will be strictly limited.
5. The consent form is that of protocol 2000-025 and its follow-up, described in protocol 2002-031
6. No additional interviews are performed.
7. There is no potential benefit for the individual of the planned urine arsenic analysis. Data on urine content of arsenic and metabolites will be analysed in batches, and therefore not being immediately available. Currently we estimate that the result of individual urine samples will be available 3-9 months after completion of pregnancy. However, the study is linked to an ongoing survey in the same area of arsenic in tube wells where mitigation activities are initiated whenever needed (RRC 2001-015). Information on arsenic content in the individual tube wells in the area (from the ongoing tube well screening) and subsequent advice has been completed for one third of the study population (September 2002) and this work will be completed in mid-2003. BRAC is the responsible partner for the mitigation activities.
8. Information from the databases created by the pregnancy food and micronutrient supplementation trial (2000-025) and its infant follow-up (2002-031) will be used. The stored urine samples will be analysed for arsenic metabolites.

ICDDR, B Centre for Health & Population Research

RRC APPLICATION FORM

RESEARCH PROTOCOL

Protocol No. 2002-029

(Revised Oct 29,2002)

FOR OFFICE USE ONLY

RRC Approval: ☐Yes / ☐No Date:

ERC Approval: ☐Yes / ☐No Date:

AEEC Approval: ☐Yes / ☐No Date:

Project Title: 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 intervention reduce the risk?*

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: Arsenic, Cognitive development, Drinking water, Methylation capacity, Nutrition interaction, Reproductive outcomes, Urinary arsenic metabolites

Relevance of the protocol: This project will generate new and highly needed knowledge on the associations between arsenic exposures and negative reproductive outcomes, such as miscarriages, stillbirths, and neonatal mortality for use in the national and international risk assessments. Further, the studies will provide answer to the question if the arsenic contamination of the drinking water already is causing excess fetal mortality. Such information is much needed in the discussion and forecasting of the arsenic-related health consequences in Bangladesh. The results will further give a solid platform for evaluation of needs for arsenic mitigation interventions.

Principal Investigator: Lars Åke Persson **Division:** PHSD **Phone:** 880-2-9885155

Address: Public Health Sciences Division **Fax No:** 880-2-8826050

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

Mohakhali, Dhaka-1212

Co-Principal Investigator(s): 1. Shams El Arifeen, ICDDR, B 2. Marie Vahter

Co-Investigator(s): Eva-Charlotte Ekstrom, Gunilla Lindmark, Sally Grantham McGregor, Anisur Rahman, Mahfuzar Rahman, Peter Kim Streatfield, Fahmida Tofail, Yukiko Wagatsuma, MA Wahed, Md Yunus

Student Investigator/Intern:

Collaborating Institute(s): Institute of Environmental Medicine, Division of Metal and Health, Karolinska Institute, and International Maternal and Child Health Unit, Uppsalla University, Sweden; Institute of Child Health, London, UK;

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

Gender

- ☒ Male
- ☒ Females

Age

- ☒ 0 – 5 years
- ☐ 5 – 9 years
- ☒ 10 – 19 years
- ☒ 20 +
- ☐ > 65

- ☒ Pregnant Women
- ☒ Fetuses
- ☐ Prisoners
- ☐ Destitutes
- ☐ Service providers
- ☐ Cognitively Impaired
  - ☐ CSW
- ☐ Others (specify _____)
- ☐ Animal

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

- ☐ Dhaka Hospital
- ☐ Matlab Hospital
- ☒ Matlab DSS area
- ☐ Matlab non-DSS 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

Proposed Sample size: Total sample size: 3000 pregnant mothers _____ ☒

Sub-group _____ ☐ _____ ☐

_____ ☐ _____ ☐

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 risk
- ☒ no more than minimal 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: US Embassy, SAREC, ICDDR, B

Yes/No

☐ ☐ Is the proposal being submitted for funding ?

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

(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	**Cost Required for the Budget Period ($)**
(Day, Month, Year - DD/MM/YY)	*a. Ist Year* *2nd Year* *3rd Year* *Other years*
Beginning date 01/06/01	
End date 01/07/04	*b. Direct Cost : US$ 359,309 Total Cost : US$ 421,020*

Approval of the Project by the Division 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.

PERSSON		1/11 2002
Name of the Division 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: 1/11 2002

Name of Contact Person (if applicable)

Table of Contents

☐ Check here if appendix is included

ROJECT 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 Åke Persson

Project Name: 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 extend can nutrition interventions reduce the risk?*

Total Budget US$ 421,020 Beginning Date 01/06/01 Ending Date 01/07/04

While it is most likely that the presence of high arsenic concentrations in the tube wells in Bangladesh will cause severe morbidity (i.e. skin lesions, cancers, lung disease, diabetes) the risk for negative reproductive outcomes is not known.

This project aims at determining the associations between arsenic exposure during pregnancy (urinary arsenic at gestational weeks 8, 14, 18 and 30) and pregnancy wastage (miscarriages, stillbirth), early neonatal death, and impaired psychomotor development in infancy. Further, we will determine if an efficient metabolism (methylation) of arsenic decrease the arsenic-induced fetal toxicity and, lastly, if early supplementation of food and multiple micronutrient supplements (as compared to routine iron-folate) decrease the arsenic-induced fetal toxicity.

Benefiting from the research infrastructure provided by the health and demographic surveillance system in Matlab, this study is nested into an ongoing food and micronutrient supplementation trial in 3000 women. It provides a unique opportunity to get a final answer to the question if arsenic exposure in pregnancy results in fetal and/or infant deaths and if the exposure damages the development of cognitive function in infancy. It will also provide information on the possible protective role of food and micronutrient supplements against arsenic toxicity. Such new knowledge would have direct relevance for the arsenic-related programs in Bangladesh and globally.

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

Name	Professional Discipline/ Specialty	Role in the Project
1. Lars Ake Persson	Epidemiologist, professor, head of Public Health Sciences Division, ICDDR,B	Principal investigator
2. Shams El Arifeen	Epidemiologist and head, Child Health Unit	Co-principal investigator
3. Eva-Charlotte Ekström	Nutrtion Epidemiologist, Clinical Sciences Division	Co-investigator
4. Mahfuzar Rahman	Environmental Epidemiologist, Public Health Sciences Division	Co-investigator
5. Anisur Rahman	Senior Medical Officer, Matlab Health Research	Co-investigator
6. Fahmida Tofail	Medical Officer, Clinical Sciences Division and the Child Development Unit	Co-investigator
7.Yukiko Wagatsuma	Child Health epidemiologist, Public Health Sciences Division	Co-investigator
8. Peter Kim Streatfield	Demographer, head of Health and Demographic Surveillance Unit	Co-investigator
9. Md. Yunus	Scientist and Head, Matlab Healht Reaearch Centre	Co-investigator
10. MA Wahed	Head, Nutrition Biochemistry Section, Clinical Sciences Division	Coo-investigator
11. Marie Vahter	Professor, Division of Metals and health, Institute of Environmental Health, Karolinska Institutet Stockholm	Co-principal investigator
12. Gunilla Lindmark	Professor and Head, International Maternal and Child Health Unit, Uppsala University, Sweden	Co-investigator
13. Sally Grantham McGregor	Professor, Institute of Child Health, London	Co-investigator
14. Allan Smith	Professor, University of Berkely, California	Consultant

DESCRIPTION OF THE RESEARCH PROJECT

Project aims and hypothesis to be tested:

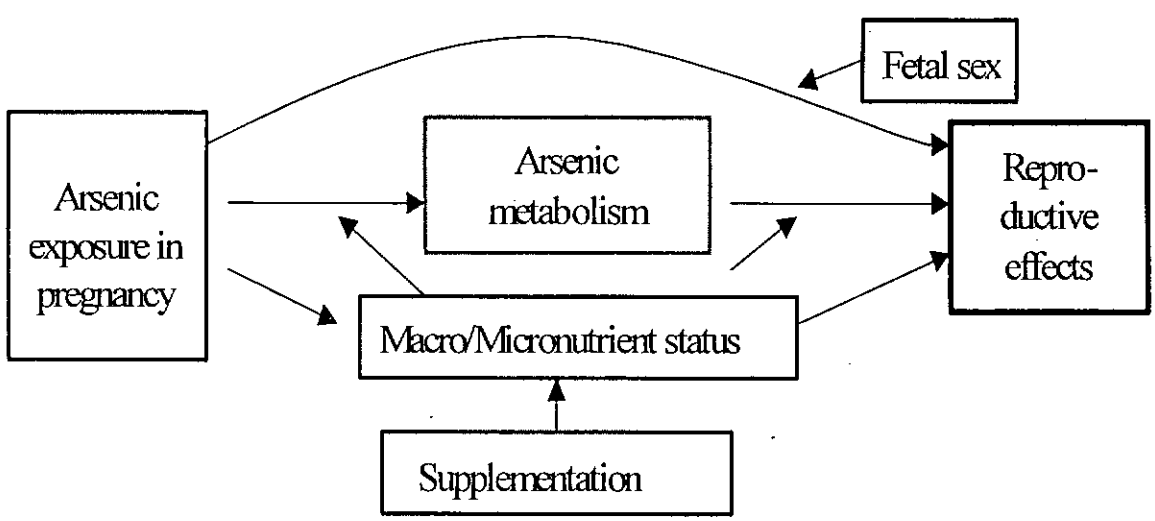
Concisely list in order, in the space provided, the hypothesis to be tested and the Specific Aims of the proposed study. Provide the scientific basis of the hypothesis, critically examining the observations leading to the formulation of the hypothesis.

This project aims at determining to what extent the current widespread ingestion of arsenic-contaminated tube-well water in Bangladesh affects reproductive outcome, in particular fetal wastage (including early miscarriage), intrauterine growth, neonatal mortality and psycho-motor development in infancy. In addition, we want to elucidate if a more efficient metabolism of arsenic (methylation) and food and micronutrient supplementation in pregnancy reduce the potential toxic effects. *The hypotheses we will test are as follows (see also Figure below):*

Laboratory-based studies and a few population-based, mainly ecological, studies suggest that arsenic exposure might seriously affect pregnancy outcome. *We postulate that consumption of arsenic contaminated water during pregnancy causes increased rate of pregnancy wastage (miscarriages, stillbirths), higher risk of early neonatal deaths, impaired intra-uterine growth, higher proportion of low birth weight and impaired cognitive development in infancy.*

Earlier studies have shown that an efficient methylation of arsenic reduces the toxicity. However, reactive and extremely toxic intermediate metabolites (trivalent methylated arsenic metabolites) may be formed. *We postulate that pregnant women with an efficient methylation of arsenic and low production of reactive intermediate metabolites are less susceptible to arsenic-induced fetal toxicity.*

There is ample evidence that nutritional factors affect pregnancy outcome. In addition, nutritional deficiencies may decrease arsenic methylation, and, eventually, increase susceptibility to toxic effects. *We postulate that pregnant women receiving food supplementation with start early in pregnancy (as compared to later) and multiple micronutrient supplementation (as compared to routine iron-folate) are less susceptible to arsenic toxicity on fetal growth and survival. These effects may be interrelated.*



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).**

An increasing number of regions, mainly in low-income countries in Asia and Latin America, have arsenic-contaminated water sources (WHO/IPCS 2001). Some 20-30 million people in Bangladesh are since 2-3 decades exposed to arsenic in their drinking water above the Bangladesh permissible levels of 50 µg/L (WHO limit 10 µg/L) (Smith et al, 2000; Rahman et al, 2001). The health consequences will be extensive and include excess cancer mortality for skin, lung, urinary bladder and kidney (NRC, 2001; WHO/IPCS 2001). Skin lesions, skin cancer, diabetes and hypertension have already been associated with arsenic exposure in Bangladesh (Tondell et al, 1999; Rahman et al, 1998; Rahman et al, 1999; Kurokawa et al, 2001). Amazingly little is known about the effects of arsenic in drinking water on human reproductive outcome, and the possible aggravating role of malnutrition. Firm evidence of negative effects in pregnancy would provide a strong incentive to reinforce ongoing mitigation activities. Understanding of the role of nutrition in toxicity of arsenic provides a rationale for intensifying ongoing supplementation programs.

Rationale for investigating effects of arsenic on reproductive outcome. Arsenic is easily transferred to the fetus (Concha et al. 1998). High doses of arsenic produce detrimental effects on the developing embryo in avian and mammalian species (Golub et al. 1998; NRC 1999). In humans, prenatal exposure to acute high doses of arsenic has resulted in miscarriage and early neonatal death (Bolliger et al., 1992). Although a few studies have addressed the potential reproductive effects of arsenic exposure in the vicinity of arsenic emitting industries and via drinking water, the evidence is not conclusive (NRC, 2001). Recently, a retrospective survey in Bangladesh (Ahmad et al. 2001) compared pregnancy outcomes in women exposed to fairly high (mean 240 µg/L) and low (below 20 µg/L) arsenic concentrations in drinking water and found increased spontaneous abortions, stillbirths, and pre-term births. However, ascertainment of exposure could be questioned and outcomes were not clearly defined. An elevation of late fetal, neonatal, and post-neonatal mortality rates was observed in northern Chile when there was a change in drinking water source leading to increase in arsenic concentration from 90 to 800 µg/L (Hopenhayn-Rich et al. 2000). A subsequent decrease in water arsenic concentrations was accompanied by a return to the normal Chilean trend in infant mortality over time, thereby supporting a causal relationship.

Men are reportedly more affected by arsenic-related health effects than women (Watanabe et al, 2001). Male fetuses may be more sensitive to chemical insult (Sakamoto et al, 2001). If this applies also for reproductive effects of arsenic needs to be elucidated.

Arsenic is only excreted in breast milk to a very limited extent (NRC, 1999). Infants in rural Bangladesh are usually breast fed for an extended period of time (1-2 years, data from HDSS, Matlab). This implies that any arsenic exposure in fetal life seizes at birth and maintained at a low level throughout infancy – even in households with arsenic contaminated drinking water. Any effect of fetal arsenic toxicity on infant growth and development is therefore not confounded by exposure in infancy. The National Research Council in the US has listed investigations into cognitive effects as a priority (NRC, 1999). A few recent cross-sectional studies have addressed arsenic exposure and cognition in school children (Siripitayakunkit et al, 1999; Calderon et al, 2001), but weakness in design make it difficult to draw inferences from those studies.

Rationale for investigating variation in arsenic metabolism. Inorganic arsenic is methylated in the body via alternating reduction of pentavalent arsenic to trivalent and addition of methyl groups from S-

adenosylmethionine (NRC 2001). The main products, monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V), are readily excreted in urine, and more efficient methylation is shown to result in a faster overall excretion of arsenic (Vahter 2000; 2002). Highly toxic reduced forms of the methylated metabolites, MMA^{III} and DMA^{III}, may be formed and have been detected in human urine (Aposhian et al 2000; Mandal et al 2001). There are marked differences in arsenic methylation, especially in the formation of MMA. Reported urinary MMA data range from a few percent in indigenous people in northern Argentina and Chile to 25-30% in Taiwan (Vahter et al, 2002). Among individuals, the percentage of MMA might vary 30-fold, whereas that of DMA often varies only 2-fold.

Experimental animal studies show that DMA is less toxic to the fetus than is inorganic arsenic (NRC, 1999). However, there is increasing evidence that formation of MMA increases arsenic toxicity. Most experimental animals methylate arsenic efficiently to DMA, with essentially no MMA being formed, and they show a faster overall excretion of arsenic than do humans (Vahter 2000; 2002). Also, people with a small percentage of urinary arsenic as MMA show less retention of arsenic than those with higher percentage MMA (Vahter 2002). In addition, recent studies indicate increasing prevalence of arsenic-related toxic effects with increasing percentage of MMA in urine (Del Razo et al. 1997; Hsueh et al. 1997; Yu et al. 2000). However, the association with human reproductive outcome has not been studied.

Rationale for investigating modifying effects of nutrition. Few studies have addressed toxicity of arsenic in malnourished populations. In an arsenic-exposed population in West Bengal body weight was negatively associated with the occurrence of keratosis (Guha Mazumder et al. 1998) and in Taiwan vascular effects (blackfoot-disease) were associated with undernourishment (high intake of sweet potatoes, low intake of rice and vegetables) (Chen et al. 1988). In Taiwan, a low serum β-carotene concentration was associated with a higher prevalence of arsenic-related skin-cancer (Hsueh et al. 1997) and ischemic heart disease (Hsueh et al. 1998). In animals a low intake of protein, choline or methionine has been shown to result in a decreased arsenic methylation and a marked increase in tissue retention (Vahter and Marafante, 1987). Zinc has been suggested to influence arsenic toxicity (NRC, 1999) and mice fed a selenium-deficient diet showed a slower elimination of arsenic than selenium-sufficient mice (Kenyon et al. 1997). Also, dietary selenium supplementation was found to prevent cytotoxic effects of arsenic mice in vivo (Biswas et al, 1999). Given that a deficiency in folate and vitamin B12 might lead to decreased levels of S-adenosylmethyltransferase (Newman 1999), it may also result in decreased methylation of arsenic. Indeed, folic acid was found to protect mouse embryo fibroblasts against cytotoxicity of arsenic (Ruan et al. 2000).

Preliminary result

Arsenic in tube wells. In a strategic pilot sample in the Matlab surveillance system, the median arsenic concentration was 144 µg/L and 25 % were above 300 µg/L . These levels have later been confirmed by an ongoing field study in Matlab.

Malnutrition.The average body weight of women in reproductive age in Matlab is 44 kg (HDSS data). Almost 3% of pregnant women in a national sample suffer from night blindness (HKI/IPHN, 1999a) and 45% are iron deficient (HKI/IPHN, 1999b), while 52% have mild and 20% moderate anemia (Ziauddin Hyder et al, 2001). Six out of ten pregnant women have low serum zinc levels (Persson, unpublished data). Studies from the 1970s to now report 47-50% low birth weight (DS Alam, and R Shaheen, unpublished data; Khan et al., 1979).

Reproductive outcome. Of the pregnancies registered in 1998 in Matlab, 89% resulted in live births, 8.1% in miscarriages, and 2.9% in stillbirths (Table 1). The number of early miscarriages is underestimated but expected to increase considerable when now urine pregnancy tests are offered to women as part of the pregnancy studies.

Table 1. Number and rates of pregnancy outcomes and early neonatal mortality in Matlab (ICDDR,B Matlab surveillance system for 1998).

Type of pregnancy outcome	*Number*	*Rate*
Total pregnancies	6486	120 per 1000 women 15-49 years
Live birth pregnancies	5776	89 % of pregnancies
Total foetal wastage	710	10% of pregnancies
Early (miscarriages)	525[1]	8.1% of pregnancies
Late (Stillbirths)	185	2.9% of pregnancies
Neonatal deaths (first month)	236	40 per 1000 live births

[1]Out of this 43% reportedly induced.

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).**

Study area. The study is performed in Matlab, where ICDDR, B is running a health and demographic surveillance system (HDSS) in 142 villages, half of which (110,000 population) is included in this study. The ground is highly affected by the sedimentation process of arsenic laden soil, as it is situated near the Meghna River. These areas in Bangladesh show the highest arsenic concentrations in tube wells (British Geological Survey, 2001). The fraction of the Matlab population that got their drinking water from tube wells increased from 55% in 1982 to 95% in 1996 (HDSS database information).

The Matlab HDSS records births, deaths, in- and out-migration, marriage, pregnancies, pregnancy outcomes and selected maternal and child health information. Community health research workers (CHRW) are updating the information on a monthly basis. In addition, socio-economic data are collected by repeated surveys. A geographic information system (GIS) is a part of the HDSS, and includes spatial information on households, tube wells, health facilities etc.

ICDDR, B has a central health facility in Matlab that receives 15,000 patients per year and supports clinical and public health research in the area. In addition, there are four sub-centers, which provide primary health care and support to studies. The NGO BRAC on behalf of the Government nutrition program provides food supplementation to pregnant women. Clinical and laboratory examinations, micronutrient supplementation administration and approximately 35% of deliveries take place in the Matlab health facilities. A notification system enables birth weight and length measurements to be performed on infants born at home within 72 hours.

Study population and procedures. This study is nested into a food and micronutrient supplementation trial, in which the effect of food and micronutrient supplementation on fetal growth and size at birth is evaluated (supported by UNICEF). We invite 3000 pregnant women to be randomized to either an early start of a 600 kcal daily food supplementation (at week 8) or the routine supplementation (later start, around wk 17). At week 14, both these groups are further randomized to either daily 60 mg iron/folate (routine); 30 iron /folate; or multiple micronutrient supplementation (UNICEF tablets, 15 micronutrients including 30 mg iron, vitamin A, zinc and selenium) (UNICEF, 1999).

Pregnancies are identified by urine test performed if amenhorroic at the time of the monthly routine home visit by the CHRW. In most cases pregnancy is detected in week 6-8. Ultrasound investigation at subcentres confirms pregnancy and time for conception. This enables detection of early fetal wastage in relation to arsenic exposure, as measured by arsenic concentration in maternal urine at the time of pregnancy test. Additional ultrasounds are done for fetal growth monitoring and clinical investigations as well as sampling of blood and urine are performed at weeks 14, 18 and 30. For women delivering at ICDDR, B facilities (estimated at 1000 women) a cord blood sample will be collected (late fetal arsenic exposure and micronutrients).

As determination of arsenic in urine is time consuming (50 samples/ week and full time technician) even with the new AFS method, we select two sampling points for the 3000 women (about 6000 samples).

Information from testing of arsenic in drinking water (about 15,000 tube wells) and individual water consumption pattern is obtained from a separate ongoing project that so far is supported by Sida and WHO. BRAC is responsible for an extensive *arsenic mitigation* component in that project.

Collection of blood and urine. Blood samples for micronutrient status will be taken in weeks 14 and 30. Urine samples will be collected in pregnancy weeks 6-8, 14, 18 and 30 for analysis of arsenic and its metabolites (indicator of recent exposure to inorganic arsenic), adjusted for variation in dilution by specific gravity. Each urine sample will be divided in two sub-samples and deep-frozen (-20°C). One of the samples will be shipped to Karolinska Institute, Stockholm, for analysis of arsenic; the other sample will be stored in tissue bank for additional analysis in the future. After training of ICDDR, B staff and technology transfer the analysis of urine samples will be performed at the biochemistry laboratory, ICDDR, B, Dhaka.

Assessment of arsenic in urine. The concentration of arsenic and its metabolites in urine will be measured by hydride generation atomic fluorescent spectroscopy (HG-AFS). Samples from all time points for 100 women will show variation in time and enable selection of two most useful time points. Urine of 3000 pregnant women will be analyzed for these two time points (totally 6000 samples). Separation of the different metabolites of inorganic arsenic in urine will be carried out on samples with elevated levels (estimated at 1500 samples) using HPLC-AFS (Le et al, 2000) and, for quality control purposes, ion exchange chromatography in combination with HG atomic absorption spectroscopy (HG-AAS).

Assessment of nutritional status. Non-pregnant weight of all women 13-44 years is available from the Matlab databases. Maternal height and repeated weights are collected during pregnancy. Micronutrient status is determined at baseline and after 16 weeks of supplementation. Plasma and red blood cell samples will be used for assessment of nutrients that may interact with toxicity (selenium, zinc), be associated deficiencies (iron, vitamin A) or related to methylation capacity (folate and B12).

Assessment of intake of food and micronutrient supplements. Compliance to food supplementation is assessed by monthly recalls, 3-day food frequency recall, and repeated 24-hour recalls. Compliance to iron-folate or multiple micronutrient supplementation is measured by pill bottles with microchip counting device in the cap monitoring tablet intake.

Assessment of potential confounders. Validated instruments assess socio-economic status, tobacco use, workload, chronic stress and determinants of compliance.

Assessment of reproductive outcome. Intrauterine growth is monitored by ultrasound at week 8, 14, 18 and 30. Birth anthropometry is measured within 72 hours. Miscarriages, stillbirths and neonatal deaths are monitored by the CHRW in monthly visits.

Assessment of cognitive development. Trained field workers will measure milestones of development monthly from 3 to 12 months of age. Trained paramedic staff will perform One-Step Means-End Support Test according to Willat (1998) at 7 months. The Bayley subscale for psychomotor development (Johnson, 1996)

will also be included at 7 months as well as a modified version of Bayley and Wolke's behavior ratings (Wolke, 1990).

Sample size. According to available information 25% of the population are exposed to relatively high arsenic concentrations in drinking water, > 300 μg/L, see below. A two group Chi 2 test with a 0,050 two-sided significance level will have 80% power to detect the difference between a lower exposure group of 70/1000 perinatal deaths and a higher exposure group of 105/1000 when the sample sizes are 2080 and 693, respectively (total 2773). Similarly, with this sample size a difference can be detected between a lower exposure group with 8% early miscarriages and a higher exposure group with 12% miscarriages. With 3000 pregnancies a 70 g difference in birth weight may be shown for each sex. A difference between high-exposure (estimated at 25% of the sample) and lower-exposure groups of 10 Psychomotor Development Index (PDI) points may be considered of clinical relevance (Moffat, 1994). However, from a public health point of view a difference of 5 PDI points may be of importance between combined and single micronutrient supplementation groups and placebo. With a level of significance of 0.05, and a power of 80%, 71 infants per group will then be sufficient. With 3000 pregnancies and 2670 live births, whereof 667 are estimated to have had a higher exposure to arsenic, the sample size would suffice would suffice to estimate effects of that size even when breaking down on nutrition intervention groups (111 in each cell of those with higher exposure).

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).**

Matlab Health Research Centre's infrastructures is presented in the text above. These facilities are unique and make this project possible. The health and demographic surveillance system will provide a lot of the necessary information needed. A strong research team has been formed with strong competence in epidemiology, arsenic epidemiology, nutrition clinical sciences, reproductive epidemiology and biochemistry. Excellent partners have been identified in the area of arsenic mitigation (BRAC) and arsenic biochemistry (professor Marie Vahter, Karolinska Institutet). The ICDDR,B biochemistry laboratory has already an AAS equipment for arsenic analysis (only total arsinic), but the procurement of another AAS equipment would considerably increase the capacity.

The subcentres are well communicated with MHRC. It takes approximately two and half hour journey from MHRC to ICRRD,B center at Dhaka. Locally, two -70^0 C freezer available for storage of biological samples along with other freezers. Also, there are two standby generators for constant electricity supply, that ensures quality storage of biological samples.

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).**

Analyses will be based on concentrations of inorganic arsenic and its metabolites in urine and fetal wastage, neonatal death, fetal growth, size at birth and psycho-motor development ratings and indices. Exposure will be modeled against outcomes in order to assess dose-effect relationship, slopes and asymptotes. These analyses will be stratified for randomization groups in order to evaluate the possible modifying effects by supplementation on pregnancy outcome as well as on methylation. Age, parity and fetal sex will be considered. Chi 2 tests will be used for dichotomous variables, while ANOVA will be used for continuous normally distributed data (i.e. birth weight). Dose-effect associations and interactions will be statistically evaluated by regression analyses with adjustments for potential confounders.

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.

This study is nested into a trial, where pregnant women are invited to participate in food and micronutrient supplementation, as well as blood sampling for micronutrients, and urine sampling for routine antenatal control (RRC 2000-025). A portion of the urine sample is stored in freezers for later arsenic analyses. The supplementation will most likely benefit the participants.

Data on urine content of arsenic and metabolites will be analyzed in batches, and therefore not being immediately available. Currently we estimate that the result of individual urine samples will be available 3-9 months after completion of pregnancy. However, the study is linked to an ongoing survey in the same area of arsenic in tube wells where mitigation activities are initiated whenever needed (RRC 2001-015). Information on arsenic content in the individual tube wells in the area (from the ongoing tube well screening) and subsequent advice has been completed for one third of the study population (September 2002) and this work will be completed in mid-2003. BRAC is the responsible partner for the mitigation activities.

Informed consent is sought, and participants are free to refrain (partly or totally) from participation in the study. The supplementation trial and urine collection have been approved by the Ethical Review Committee at ICDDR, B, Dhaka, Bangladesh (RRC 2000-025). An additional review, including full plan for the arsenic analysis and reproductive outcome is now submitted to the Ethical Review Committee in October 2002. The proposal will also be reviewed at the Regional Ethical Committee at the Karolinska Institutet, Stockholm, Sweden.

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.

The findings will be communicated to other actors and stakeholders in the area of arsenic contamination of ground water and effects on reproductive outcome in Bangladesh. This will be done through reports (popular as well as scientific) and through a workshop with invited participants at the Matlab Training Centre during the second year of the project.

The findings will be used in order to recommend appropriate actions in order to protect fetuses and newborns.

A narrative and financial report will be submitted to funding partners every 6 months. After completion of the project (at 24 months) a final report will be submitted to the funding agencies within another 2 monts.

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)**

ICDDR,B and the Matlab surveillance system and research infrastructure offer unique possibilities for the planned studies with strong competence in epidemiology, nutrition, reproductive health and biochemistry. The research team at Institute of Environmental Medicine, Karolinska Institutet has long experience in arsenic exposure and toxicity research and has modern analytical equipment, e.g. HPLC-HG-AFS, HG-AAS, and ICP-MS. As part of the project a knowledge transfer will take place, so that urine analysis of total arsenic metabolites is performed at the ICDDRB laboratory from second half of 2003. International Maternal and Child Health, Uppsala University (Professor Gunilla Lindmark) has reproductive health expertise for the analyses of fetal wastage outcome. Professor Allan Smith at Berkely, CA, has participated in the initial discussions of the project and will participate in the analytical and write-up phase. Professor Sally Grantham McGregor at Institute of Child Health, London, is assisting the project on the child development component and is also consultant and mentor to the Child Development Unit at ICDDR,B. She has extensive experience of development assessments and studies of nutrition and cognitive development.

ICDDR,B PI *Lars Åke Persson* Epidemiologist, Head of Public Health Sciences Division. Co-PI *Shams El Arifeen*, Epidemiologist and Head, Child Health Unit. Co-investigator *Eva-Charlotte Ekström*, Nutrition epidemiologist, Clinical Sciences Division. Co-investigator *Mahfuzar Rahman*, Environmental epidemiologist, Public Health Sciences Division. Co-investigator *Anisur Rahman*, Public Health Physician, Co-investigator *Peter Kim Streatfield*, Demographer, Head, Surveillance Unit. Co-investigator *Yukiko Wagatsuma*, Epidemiologist, responsible for fetal ultrasound measurements. Co-investigator *Fahmida Tofail*, Medical Officer, Child Development Unit, Co-investigator *Md. Yunus*, Scientist and Head, Matlab. Co-investigator *MA Wahed*, Head, Nutrition Biochemistry Section.

Karolinska institutet. Co-principal investigator *Marie Vahter*, toxicologist, professor, Head of Division of Metals and Health, Institute of Environmental Medicine. Laboratory technician *Barbro Nermell*, responsible for arsenic speciation and training of ICDDRB staff, Division of Metals and Health, Institute of Environmental Medicine.

Additional collaboration. Co-investigator *Gunilla Lindmark* Reproductive health specialist, professor and Head, International Maternal and Child Health Unit, Uppsala University. Consultant *Allan Smith*,

Epidemiologist, professor, University of Berkely, Calif. Co-investigator *Sally Grantham McGregor*, Professor, Institute of Child Health, London.

Budget Justifications

Please provide one page statement justifying the budgeted amount for each major item. Justify use of man power, major equipment, and laboratory services.

This study is nested into the ongoing supplementation project, fully funded by UNICEF. Funds are requested to cover the specific cost for this arsenic component as outlined below. In early 2004 analyses of arsenic exposure and early miscarriages are due, and in late 2004 final scientific reports will be prepared for scientific journals, meetings and a dissemination workshop in Matlab.

Activity	Jan-June 2002	Jul-Dec 2002	Jan-Jun 2003	Jul-Dec 2003	Jan-Jun 2004
Recruitment pregnant women					
Pregnancy follow-up					
Follow-up infants to 12 m					
Analyses					
Reporting					

Professional staff. *Lars Åke Persson* has initiated the study and is having the overall responsibility for the fieldwork and the later analytical work and write up. *Shams Arifeen* is child health epidemiologist and expert on intrauterine and post-natal growth. *Eva-Charlotte Ekström* is nutritionist and nutrition epidemiologist and has taken the lead regarding nutrition-arsenic interactions. *Mahfuzar Rahman* is environmental epidemiologist and is overseeing the practical implementation of different steps in the study. *Yukiko Wagatsuma* is epidemiologist with responsibility for the ultrasound component in the pregnancy study. *Mr Wahed* is head of our biochemistry laboratory, where the arsenic analysis of urine samples will be built up with assistance from Karolinska Institute. *Anisur Rahman* is public health physician and epidemiologist in Matlab, and responsible for the day-to-day back up and trouble-shooting for the study. The study is also supported by Dr Md Yunus and J Chakraborty, who are responsible for the Matlab operations overall, and the service activities in the field, respectively (covered by ICDDRB). *Fahmida Tofail* is working in the Child Development Unit and has the immediate responsibility for setting up the assessment of motor milestones and assessment of cognitive development. *Peter Kim Streatfield* is head of the Health and Demographic Surveillance Unit and has the overall responsibility for the integration and use of surveillance data in the project.

Field and laboratory staff. A lab technician in Matlab is handling the urine and blood samples and the time allocated to this component is estimated at 6 months. A laboratory officer in Dhaka is designated for the analyses of urine samples and will be trained at Karolinska Institute in the relevant technique from September 2002. In the field urine samples are collected at home visits when pregnancy is identified and thereafter at 4 visits to sub-centres.

Operating expenses. In addition to analyses of total arsenic in urine arsenic speciation costs are covered by Karolinska Institute. The micronutrient analyses are proposed to be performed in a subsample of 2x1000 samples at a unit cost of 25 dollars.

ARSENIC in MINIMAT STUDY, Matlab, 2002-2004

Salaries incl. benefits and income taxes		Rate/m	US Embassy	ICDDRB	SAREC	US Embassy	ICDDRB/	SAREC	
Sep-02		$	months	months	months				Total
Professional staff	Name		units	units	units	dollar	dollar	dollar	cost
Epidemiologist, PI,	LÅ Persson	14116	0.5	1	1	7,146	14,292	14,292	21,439
Child health epidemiologist	Shams El Arifeen	7533	0.5	1	1	3,814	7,627	7,627	11,441
Nutrition epid. consultant P4	Eva-Charlotte Ekström	4667	1.0	0	2	4,725	0	9,451	14,176
Arsenic epidemiologist, NOC*	Mahfuzar Rahman	1025	1.0	3	1	1,038	3,113	1,038	5,189
Epidemiologist/ultrasound	Yukiko Wagatsuma	8661	1.0	1	1	8,769	4,385	8,769	21,923
Head, arsenic lab NOC*	Mr Wahed	1525	1.0	0	1	1,544	0	1,544	1,544
Public health physician	Anisur Rahman	1150	1.0	0	1	1,164	0	1,164	1,164
Head, Matlab	Md Yunus	2475	-	0	1	0	0	2,506	0
Senior manager, NOC*	J Chakraborti	1467	-	0	1	0	0	1,485	0
Subtotal professional staff						*28,201*	*29,418*	*47,877*	*76,876*
Field and laboratory staff								0	
Senior Lab Technician, Matlab,GS4		269	6.0			1634	0	0	1634
Arsenic lab officer, Dhaka,GS5		353	12.0	-	12.0	4289	0	4289	4289
Field manager, NOA		679	6.0			4125	0	0	4125
Senior Field Research Assisstant, GS4		269	48.0			13073	0	0	13073
Senior Health Research Assistant, GS4		269	72.0			19610	0	0	19610
Field Research Assistants,GS3		225	120.0			27338	0	0	27338
Child development research assistant GS6		459	48.0	24.0		22307	11154	0	
Data Management, GS6		459	6.0			2788	0	0	2788
Data Management Assistant, GS 3		225	12.0			2734	0	0	2734
Subtotal field staff						*97899*	*11154*	*4289*	*75591*
Operating expenses		Rate $							-
Urine total arsenic incl specific gravity		12	5000	0	1000	60000	0	12000	60000
Micronutrient analyses		25	2000	0	0	50000	0	0	50000
Subtotal operating expenses						*110000*	*0*	*12000*	*110000*
Trvael									
Dhaka-Stockholm-Dhaka		1400			4			5,600	5600
Stipend		1000			10			10,000	10000
Subtotal								*15600*	*15600*
Capital expenditures									
Freezer -70		8500			1			8,500	8500
Subtotal other expenditure						*0*	*0*	*8,500*	*8,500*
Other expenditures									
Printing, photocopies						1,000	500	0	1,500
Training and dissemination						250	500	0	750
Communication (e mail fax phone)						0		0	0
Unforeseen expenditures						0		0	2,000
Subtotal other expenditure						*1,250*	*1,000*	*0*	*4,250*
Total direct cost						237,349	41,571	88,266	367,187
Common operating costs						61,711	0	22,067	83,777
Total						299,060	41,571	110,333	450,964

Salaries adjusted for 1.25% average increase during project period

Total project cost **450,964**

31/10/02

Md. Bozlur Rahman
Manager, Finance & Pay
ICDDR,B
Health & Population Research
Mohakhali, Dhaka 1212
Bangladesh

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 ☐
8. Ethical Assurance ☐
9. Consent Forms ☐
10. Detailed Budget ☐

ICDDR,B: Centre for Health and Population Research

Combined Interventions to Promote Maternal and Infant Health

VERBAL CONSENT FORM

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, Cornell University of USA and UNICEF, is undertaking a study to improve maternal and infant nutritional status. The study will assist in the ongoing "Pushti" program by helping some of you to start the feeding program earlier, to provide with either iron tablets at standard or half doses, or a mix of 15 vitamins and minerals including half dose of iron. This mix has been specially produced by UNICEF for pregnant women. These tablets will be given to you today in bottles, which you can take home. The decision on who will receive what will be decided at random (by chance). After the birth of your child, we will provide you with either counseling to help you with breast-feeding your baby or health education on care for yourself and the baby.

If you agree to participate, we and other members of our team will visit you several times when you are pregnant and also after the birth of your child until the baby is 12 months old. We will also request you to visit the ICDDR,B sub-centre at least 4 times during pregnancy. In the sub-centre, we will give you a full antenatal check up, including physical and pelvic examination and ultrasonographic monitoring of the baby inside you. We will also collect 5.5 ml of blood (about a tea spoonful) from your veins two times and once from a finger prick. We will test this blood for anaemia, and status of other vitamins and minerals. On your first visit to the sub-centre, if you agree, we will test whether you have an infection in the vagina, which is known to result in early delivery of babies. If you have the infection, but do not have an abnormal vaginal discharge then you will either receive a seven-day treatment course with a drug called metronidazole or with something that will look similar to it but will not have the drug. No one will know who will receive what which will decided by chance. Sometimes people taking this drug experience a metallic taste in the mouth, nausea, headache and dry mouth.

We will set up a system so that we will be able to measure the weight, length and other measurements of your newborn soon after birth. We will request your family to notify us immediately after birth so that we can do this. We will reimburse you for cost incurred. We will check on your physical condition after birth to assess if you have any health problems and provide necessary management. We will visit you to take the weight and length of your child once every month till 6 months of age, and every 2 months thereafter till 12 months of age. We will also ask you about feeding and health of the baby.

The purpose of doing all this is to assess the benefit of the food and micronutrient supplementation, treatment of the infection in the vagina, and of the breastfeeding counseling. The information that will be available from this will help the policy makers to decide on the best way to provide these services for communities like ours.

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.

In general, we have to be careful about what medicines and drugs are taken during pregnancy. What we will offer you, under the conditions of the study, has been found to be safe. However, if you have any questions about these or any other aspect of the study we will be happy to discuss them with you. 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. Also, once you have agreed to take part in the study, you may remove yourself or your child from the study at any time without any penalty or change in the routine care you or your child receives. You will still receive our routine care and necessary support and treatment.

Once you have agreed to participate in the study, you can contact your home healthcare worker if you have any problems or questions. You may also contact the 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 understand what this study is doing? Yes No
- Do you agree to participate in this study? Yes No

Date: _____

_____

Signature of Community Health Research Worker (CHRW)

ICDDR,B: Centre for Health and Population Research

Combined Interventions to Promote Maternal and Infant Health

মৌখিক সম্মতি প্রত্র

গর্ভকালীন অবস্থায় মায়ের যথাযথ পুষ্টি বিধান 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। এই অপুষ্টির 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, যুক্তরাষ্ট্রের কর্ণেল ইউনিভার্সিটি ও ইউনিসেফ এর সহযোগিতায় একটি গবেষণা প্রকল্প হাতে নিতে যাচ্ছে যা মা ও শিশুর পুষ্টি অবস্থার উন্নতি সাধন করবে। এই প্রকল্পের আওতায় চলতি 'পুষ্টি' কর্মসূচিকে সহযোগিতা করে আপনাদের মধ্যে কাউকে কাউকে শীঘ্র পুষ্টি কর্মসূচিতে অংশগ্রহণ করতে সাহায্য করা হবে, কেউ সাভাবিক বা অর্ধেক মাত্রায় আয়রণ ট্যাবলেট পাবে অথবা ১৫টি ভিটামিন ও খনিজ পদার্থ মিশ্রণ সম্বলিত একটি ট্যাবলেট পাবে (যার মধ্যে অর্ধেক মাত্রায় আয়রণ অন্তর্ভুক্ত) এর মাধ্যমে এই গবেষণাটি চলতি 'পুষ্টি' কর্মসূচিকে সহযোগিতা করবে। ইউনিসেফ ভিটামিন এবং খনিজের এই সংমিশ্রণটি গর্ভবতী মহিলাদের জন্য বিশেষ ভাবে তৈরী করেছে । এই ট্যাবলেটগুলো আপনাদেরকে বোতলে ভরে দেয়া হবে যা আপনারা বাসায় নিয়ে যেতে পারবেন। কে কোন ধরণের ট্যাবলেট পাবে তা লটারীতে নির্ধারণ করা হবে। শিশুর জন্মের পর আমরা আপনাকে শিশুকে বুকের দুধ খাওয়ানোর ওপর পরামর্শ দেব অথবা শিশুর যত্নের বিষয়ে স্বাস্থ্য পরামর্শ প্রদান করব।

আপনি যদি এই গবেষণায় অংশগ্রহণে সম্মত হন তবে আমরা এবং আমাদের দলের অন্যান্য সদস্যরা আপনার গর্ভকালীন সময়ে এবং আপনার শিশুর জন্মের পর তার ১২ মাস বয়স পর্যন্ত কয়েকবার আপনার সাথে সাক্ষাত করব। গর্ভবস্থায় মোট ৪ বার আই সি ডি ডি আর, বি-র স্বাস্থ্য কেন্দ্রে যাওয়ার জন্য আমরা আপনাকে অনুরোধ করব। স্বাস্থ্য কেন্দ্রে আমরা আপনাকে শারীরিক পরীক্ষা সহ গর্ভকালীন সকল পরীক্ষা-নিরীক্ষা করব, আলটাসনোগ্রামের মাধ্যমে জরায়ুর ভেতরে শিশুর পর্যবেক্ষণ করব। আমরা দুই বার আপনার শিরা থেকে ৫.৫ মি.লি. (প্রায় এক চা চামচের সমান) এবং একবার আঙ্গুলের মাথা থেকে রক্ত সংগ্রহ করব। এই রক্ত পরীক্ষা করে আমরা আপনার রক্তশূণ্যতা এবং অন্যান্য ভিটামিন ও খনিজ লবণের অবস্থা জানব। আপনি প্রথমবার স্বাস্থ্য কেন্দ্রে এলে, এবং সম্মত হলে, আমরা পরীক্ষা করে দেখব আপনার যোনীর কোন সংক্রমন আছে কিনা যার ফলে সময়ের আগেই শিশুর জন্মদান ঘটে। আপনার যোনীর এই সংক্রমন পাওয়া গেলে এবং কোন অস্বাভাবিক স্রাব না থাকলে আপনাকে হয় মেট্রোনিডাজল ঔষধ দিয়ে সাতদিনের চিকিৎসা দেয়া হবে বা একই রকম দেখতে কিন্তু যার মধ্যে ঐ ঔষধ নাই তা দেয়া হবে। কেউ জানবে না কে কি পাবে - লটারীর মাধ্যমে তা নির্ধারণ করা হবে। কখনও কখনও এই ঔষধ খেলে মুখে ধাতব স্বাদ, বমিবমি ভাব, মাথাব্যথা বা মুখ শুকিয়ে যাওয়ার মতো উপসর্গ দেখা দিতে পারে।

আমরা এমন একটি ব্যবস্থা গ্রহণ করব যার মাধ্যমে জন্মের পর পরই আপনার শিশুর ওজন, দৈর্ঘ্য ও অন্যান্য মাপ করা যাবে। আপনাকে ও আপনার পরিবারকে আমরা অনুরোধ করব যে শিশুর জন্মের পর পরই আপনারা আমাদের জানাবেন যাতে আমরা একাজটি করতে পারি । এর জন্য আপনাদের যা খরচ হবে আমরা তা পরিশোধ করে দেব। আপনার শিশুর জন্মের পর আপনার শারীরিক অবস্থা আমরা পরীক্ষা করে দেখব এবং কোন শারীরিক সমস্যা থাকলে তার জন্য প্রয়োজনীয় ব্যবস্থা প্রদান করব। আপনার শিশুর ৬ মাস বয়স পর্যন্ত প্রতি মাসে একবার এবং এরপর প্রতি দুই মাস পর পর তার ১২ মাস বয়স পর্যন্ত আমরা আপনার শিশুর ওজন এবং দৈর্ঘ্য মাপার জন্য আসব। এছাড়া আপনার শিশু খাওয়া-দাওয়া এবং স্বাস্থ্য সম্পর্কেও আমরা জিজ্ঞাসা করব।

এই সব করার মূল উদ্দেশ্য হলো পুষ্টি খাদ্য ও ভিটামিন/খনিজ পদার্থ, গর্ভাবস্থায় সংক্রমনের চিকিৎসা, এবং বুকের দুধ খাওয়ানোর পরামর্শদানের উপকারিতা যাচাই করা। এ থেকে আমরা যে তথ্য পাব তা আপনাদের জন্য এ সকল সেবা প্রদানের সব চেয়ে ভাল পন্থাটি বাছাই করতে সহায়ক হবে।

আমরা আপনাকে নিশ্চয়তা দিচ্ছি যে 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 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।

আমাদের গর্ভকালীন সময়ে যে কোন ঔষধ খাওয়ার ব্যাপারে সাবধানতা অবলম্বন করা উচিত। আমরা আপনাকে এই গবেষণা কাজের জন্য যাযা দেবো সেগুলি নিরাপদ হিসাবে প্রমানিত হয়েছে। তারপরও আপনি এই গবেষণা সম্পর্কে যে কোন প্রশ্ন আমাদের করতে পারেন এবং আমরা আনন্দের সাথে তার জবাব দেব। এই কাজে আপনার অংশগ্রহন সম্পূর্ণ স্বেচ্ছামূলক। কোন রকম দায়বদ্ধতা ছাড়াই এই গবেষণা থেকে যে কোন সময়ে সরে আসার সম্পূর্ন স্বাধীনতা আপনার আছে। আপনি যদি এই গবেষণায় অংশগ্রহন নাও করেন তবুও আপনি ও আপনার পরিবারের আই সি ডি ডি আর, বি থেকে কোন চিকিৎসার ত্রুটি হবে না। এবং একবার এই গবেষণায় অংশগ্রহনে সম্মত হওয়ার পরও আপনি চাইলে যে কোন সময় এই গবেষণা থেকে আপনি নিজে কিংবা আপনার সন্তানের অংশগ্রহন প্রত্যাহার করে নিতে পারেন এবং তাতেও নিয়মিত যে সেবা আপনি কিংবা আপনার সন্তান পেয়ে আসছেন তার কোন পরিবর্তন হবে না । আপনি বরাবরের মতই আমাদের নিয়মিত সেবা এবং প্রয়োজনীয় সহযোগিতা ও চিকিৎসা পেয়ে যাবেন।

এই গবেষণায় অংশগ্রহনে সম্মত হওয়ার পর আপনি যে কোন সমস্যা বা প্রশ্নের জন্য আপনার এলাকার স্বাস্থ্যকর্মীর সাথে যোগাযোগ করতে পারবেন। আপনি আই সি ডি ডি আর, বি মতলব হাসপাতালেও যোগাযোগ করতে পারেন অথবা ডাঃ লার্স অকে পারসনের সাথে নিচের ফোন নম্বরে যে কোন সময় যোগাযোগ করতে পারেনঃ ৯৮৮ ৫১৫৫ (ঢাকা)

- আপনার কি কোন প্রশ্ন আছে ? হ্যাঁ না
- আপনি কি বুঝতে পেরেছেন এই গবেষণা কি নিয়ে কাজ করছে? হ্যাঁ না
- আপনি কি এই গবেষণায় অংশগ্রহনে সম্মত আছেন ? হ্যাঁ না

তারিখঃ _____

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স্বাস্থ্য কর্মীর স্বাক্ষর

Version: October 29, 2002

ICDDR,B: Centre for Health and Population Research

Combined Interventions to Promote Maternal and Infant Health

WRITTEN CONSENT FORM

Thank you for participating in the study. I am sure you remember the details about 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, Cornell University of USA and UNICEF, is undertaking a study to improve maternal and infant nutritional status. The study will assist in the ongoing "Pushti" program by helping some of you to start the feeding program earlier, to provide with either iron tablets at standard or half doses, or a mix of 15 vitamins and minerals including half dose of iron. This mix has been recommended by UNICEF. These tablets will be given to you today in bottles, which you can take home. The decision on who will receive what will be decided at random (by chance). After the birth of your child, we will provide you with either counseling to help you with breast-feeding your baby or health education on care for yourself and the baby.

If you agree to participate, we will give you a full antenatal check up, including physical and pelvic examination and ultrasonographic monitoring of the baby inside you. We will also collect 5.5 ml of blood (about a teaspoonful) from your veins two times and once from a finger prick. We will test this blood for anaemia, and status of other vitamins and minerals. If you agree, we will collect a swab from your upper vagina and will test it to see whether you have an infection in the vagina, which is known to result in early delivery of babies. If you have the infection, but do not have an abnormal vaginal discharge then you will either receive a seven-day treatment course with a drug called metronidazole or with something that will look similar to it but will not have the drug. No one will know who will receive what which will decided by chance. We will also request you to visit this clinic at least 3 more times during pregnancy. We will repeat the same things when you come again and vaginal swab will also be taken for one more time at the sixth months of pregnancy to see whether you have been properly treated with the medicine. On every clinic visit, we will store part of the urine that is collected for routine antenatal check-up and store it for eventual testing for the presence of arsenic in it.

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)

Signature/thumb impression of pregnant woman

Date: _____

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লিখিত সম্মতি পত্র

এই গবেষণা কাজে অংশগ্রহনের জন্য আপনাকে ধন্যবাদ। আপনার নিশ্চয়ই এই গবেষণা কাজ সম্পর্কে সব কিছু মনে আছে, তারপরও আপনার সুবিধার জন্য কিছু তথ্য আমি আবার বলছি।

গর্ভকালীন অবস্থায় মায়ের যথাযথ পুষ্টি বিধান 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। এই অপুষ্টির 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, যুক্তরাষ্ট্রের কর্ণেল ইউনিভার্সিটি ও ইউনিসেফ এর সহযোগিতায় একটি গবেষণা প্রকল্প হাতে নিতে যাছে যা মা ও শিশুর পুষ্টি অবস্থার উন্নতি সাধন করবে। এই প্রকল্পের আওতায় চলতি 'পুষ্টি' কর্মসূচিকে সহযোগিতা করে আপনাদের মধ্যে কাউকে কাউকে শীঘ্র পুষ্টি কর্মসূচিতে অংশগ্রহণ করতে সাহায্য করা হবে, কেউ সাভাবিত বা অর্ধেক মাত্রায় আয়রণ ট্যাবলেট পাবে অথবা ১৫টি ভিটামিন ও খনিজ পদার্থ মিশ্রণ সম্বলিত একটি ট্যাবলেট পাবে (যার মধ্যে অর্ধেক মাত্রায় আয়রণ অন্তর্ভুক্ত) এর মাধ্যমে এই গবেষণাটি চলতি 'পুষ্টি' কর্মসূচিকে সহযোগিতা করবে। ইউনিসেফ ভিটামিন এবং খনিজের এই সংমিশ্রণটি গর্ভবতী মহিলাদের জন্য বিশেষ ভাবে তৈরী করেছে । এই ট্যাবলেটগুলো আপনাদেরকে বোতলে ভরে দেয়া হবে যা আপনারা বাসায় নিয়ে যেতে পারবেন। কে কোন ধরণের ট্যাবলেট পাবে তা লটারীতে নির্ধারণ করা হবে। শিশুর জন্মের পর আমরা আপনাকে শিশুকে বুকের দুধ খাওয়ানোর ওপর পরামর্শ দেব অথবা শিশুর যত্নের বিষয়ে স্বাস্থ্য পরামর্শ প্রদান করব।

আপনি যদি সম্মত হন তবে আমরা আজ স্বাস্থ্য কেন্দ্রে আপনাকে শারীরিক পরীক্ষা সহ গর্ভকালীন সকল পরীক্ষা-নিরীক্ষা করব, এবং আলটাসনোগ্রামের মাধ্যমে আপনার গর্ভের ভেতরের শিশুকে পর্যবেক্ষণ করব। আমরা দুই বার আপনার শিরা থেকে ৫.৫ মি.লি. (প্রায় এক চা চামচের সমান) এবং একবার আঙ্গুলের মাথা থেকে রক্ত সংগ্রহ করব। এই রক্ত পরীক্ষা করে আমরা আপনার রক্তশূণ্যতা এবং অন্যান্য ভিটামিন ও খনিজ লবণের অবস্থা জানব। আপনি সম্মত হলে, আমরা আজ আপনার যোনীর উপরিভাগ থেকে পরীক্ষার জন্য সোয়াব সংগ্রহ করব এবং পরীক্ষা করে জানব যে যোনীর কোন সংক্রমন আছে কিনা যার ফলে সময়ের আগেই শিশুর জন্মদান ঘটে। আপনার যোনীর এই সংক্রমন পাওয়া গেলে এবং কোন অস্বাভাবিক স্রাব না থাকলে আপনাকে হয় মেট্রোনিডাজল ঔষধ দিয়ে সাতদিনের চিকিৎসা দেয়া হবে বা একই রকম দেখতে কিন্তু যার মধ্যে ঐ ঔষধ নাই তা দেয়া হবে। কেউ জানবে না কে কি পাবে - লটারীর মাধ্যমে তা নির্ধারণ করা হবে। আমরা গর্ভকালীন সময়ে অন্ততঃ আরো তিনবার এই ক্লিনিকে আসার জন্য আপনাকে অনুরোধ করব। আপনি যখন আবার আসবেন তখন আজকের সবকিছুই আমরা আবার করব। ছয়মাসের গর্ভাবস্থায় আর একবার যোনী থেকে সোয়াব সংগ্রহ করব - ঔষধ খাওয়ার পর আপনি কতটুকু ভাল হয়েছেন তা দেখার জন্য। প্রতিবার ক্লিনিকে নিয়মিত গর্ভকালীন পরীক্ষার জন্য যে প্রসাব আপনার কাছ থেকে নেয়া হবে আমরা তার কিছু অংশ সংগ্রহ করে রাখব এবং পরবর্তীতে আর্সেনিক আছে কিনা এই প্রসাব পরীক্ষা করে দেখা হবে।

আমরা আপনাকে নিশ্চয়তা দিচ্ছি যে 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 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 অংশগ্রহন সম্পূর্ণ স্বেচ্ছামূলক। কোন রকম দায়বদ্ধতা ছাড়াই এই গবেষণা থেকে যে কোন সময়ে সরে আসার পূর্ণ স্বাধীনতা আপনার আছে । আপনি যদি এই গবেষণায় অংশগ্রহন নাও করেন তবুও আপনি ও আপনার পরিবারের আই সি ডি ডি আর, বি থেকে কোন চিকিৎসার ত্রুটি হবে না। একবার এই গবেষণায় অংশগ্রহনে সম্মত হওয়ার পরও আপনি চাইলে যে কোন সময় এই গবেষণা থেকে আপনি নিজে কিংবা আপনার সন্তানের অংশগ্রহন প্রত্যাহার করে নিতে পারেন এবং তাতেও নিয়মিত যে সেবা আপনি কিংবা আপনার সন্তান পেয়ে আসছেন তার কোন পরিবর্তন হবে না । আপনি বরাবরের মতই আমাদের নিয়মিত সেবা এবং প্রয়োজনীয় সহযোগিতা ও চিকিৎসা পেয়ে যাবেন।

আপনি এই গবেষণা সংক্রান্ত যে কোন প্রশ্ন আমাদের করতে পারেন এবং আমরা আনন্দের সাথে তার জবাব দেব। আপনি যে কোন সমস্যা বা প্রশ্নের জন্য আপনার পারিবারিক স্বাস্থ্যকর্মীর সাথে যোগাযোগ করতে পারবেন।

এই গবেষণা সম্পর্কে আপনার কোন প্রশ্ন থাকলে আমি সানন্দে তার উত্তর দেব। আপনি আই সি ডি ডি আর, বি মতলব হাসপাতালেও যোগাযোগ করতে পারেন অথবা ডাঃ লার্স অকে পারসনের সাথে নিচের ফোন নম্বরে যে কোন সময় যোগাযোগ করতে পারেনঃ ৯৮৮ ৫১৫৫ (ঢাকা)

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

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স্বাক্ষীর স্বাক্ষও (প্যারামেডিক) গর্ভবতী মায়ের স্বাক্ষর/টিপসই

তারিখ ঃ_____

13 November 2002

Review of Protocol # 2002-029 `The Bangladesh arsenic calamity and reproduction: Does arsenic contamination of drinking water result in fetal wastage, intra uterine growth retardation, neonatal deaths and impaired cognitive development and to what extent can nutrition intervention reduce risk?
PI: Prof. Lars Ake Persson

In earlier ERC approved protocols # 2002-025 and follow up of that protocol # 2002-031; pregnant women were invited to participate in food and micronutrients supplementation as well as blood sampling for micronutrients and urine sampling for routine anti-natal control. A portion of the antenatal routine urine sample was stored in freezers for later arsenic analysis, which was also approved by ERC.

The present protocol does not imply collection of any additional information or samples but describes the use of the urine samples earlier collected for arsenic estimation and analysis in relation to outcomes described in protocols 2002-25 and 2002-031.

There will be no new participants (except those of protocols 025 and 031). No additional interviews will be performed. Consent forms are those of earlier protocols, no new consent form will be necessary.
Thus the study does not imply any risk to the participants.

In the face sheet, ~~4(e)~~ 3(c); should be marked yes. `Yes' marking in ~~3 (e)~~ 4(h) and 5 (a) and (b) may be qualified to indicate use of earlier samples or consent form.

The protocol may be recommended for ethical clearance.

Thanking you

(Prof. A.K.M. Nurul Anwar)
Member, ERC