International Centre for Diarrhoeal Disease Research, Bangladesh
CENTRE FOR HEALTH AND POPULATION RESEARCH
Mail : ICDDR, B, GPO Box 128, Dhaka-1000, Bangladesh
Phone: 880-2-881175[illegible]-60, Telex : 642486 ICDD BJ
Fax : 880-2-8823116, 8812530, 8811568, 8826050, 9885657, 8811686, 8812529
Cable : Cholera Dhaka

Memorandum

12 November 2003

To : Dr. Ali Miraj Khan
PI of research protocol # 2003-037
Clinical Sciences Division

From: Professor AKM Nurul Anwar
Chairman
Ethical Review Committee (ERC)

Sub : Approval of research protocol # 2003-037

This is in reference to your memo dated 10th November 2003 with the modified version of your research protocol # 2003-037 titled "Introduction of routine zinc therapy for children with diarrhoea safety compliance and acceptability". 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 29th October 2003.

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.

cc: Associate Director
Clinical Sciences Division

CENTRE FOR HEALTH AND POPULATION RESEARCH

Clinical Sciences Division

Memorandum

Date: 10 November 2003

To: Chairman, ERC

From: Dr Ali Miraj Khan
PI, Protocol # 2003—037

Sub: Submission of Protocol (revised version) # 2003—037

This is to inform you that we have revised the protocol entitled "Introduction of routine zinc therapy for children with diarrhoea: safety, compliance and acceptability" taking into account the comments of the ERC reviewers.

We would appreciate very much if you could consider it for approval.

Thank you.

The suggestions made by ERC have been incorporated.
12.11.03

(Project Title: INTRODUCTION OF ROUTINE ZINC THERAPY FOR CHILDREN WITH DIARRHEA: SAFETY, COMPLIANCE & ACCEPTABILITY)

RESPONSE TO COMMENTS OF ERC

a) ERC face sheet : Corrections have been done according to suggestions.

b) Information under 'Section for Ethical assurance' : all the issues pointed out by reviewer have been addressed and the section has been rewritten (Page no.13-14).

c) Both English and Bengali version of consent form have been modified according to suggestions given (page no. 28-29).

Ashkar.

International Centre for Diarrhoeal Disease Research, Bangladesh
CENTRE FOR HEALTH AND POPULATION RESEARCH
Mail : ICDDR,B, GPO Box 128, Dhaka-1000, Bangladesh
Phone: 880-2-8811751-60, Telex : 642486 ICDD BJ
Fax : 880-2-8823116, 8812530, 8811568, 8826050, 9885657, 8811686, 8812529
Cable : Cholera Dhaka

Memorandum

2 November 2003

To : Dr. Ali Miraj Khan
PI of the research protocol # 2003-037
Clinical Sciences Division

From: Professor AKM Nurul Anwar
Chairman, Ethical Review Committee (ERC)

Sub : Research protocol # 2003-037

Thank you for your research protocol # 2003-037 titled "Introduction of routine zinc therapy for children with diarrhoea safety compliance and acceptability", which the ERC considered in its meeting held on 29th October 2003. After review and discussion, the Committee made following observations on the protocol:

a) On the ERC Face Sheet, item 2(a), 2(d), 4(c), and 4(d) should be marked 'YES'.

b) Information provided under 'Section for Ethical Assurance' was considered to be inadequate. The investigators should briefly mention under this section about the steps to be followed to manage possible side effects, both at hospital and in the community. The investigators could also discuss about minimum/no risk of zinc toxicity with the proposed dose. There was no discussion whether zinc would be stopped if vomiting is more than 4 times or more/hour. Further, investigators mentioned '*if a child who had not vomited in past 6 hours, vomited within 60 minutes of receiving zinc would be recorded as an adverse effect.*' But it was not clarified whether in such situation zinc would be stopped or not. This section should also contain the issues regarding confidentiality, clients' rights, benefits, and anonymity of the study participants.

c) Consent form: In the English version of the consent form, the caregiver should be assured that possible side effects would be managed accordingly and they need to bring the child if problems encounter at home. The consent form should contain provision for obtaining thumb impression of illiterate study participants. Some Bengali translations are not appropriate (for instance, 'will not involve any invasion of your privacy or sensitive aspects of your behaviour.....) Further, spelling mistakes should be corrected in the Bangla version of the consent form.

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

Thank you once again.

Copy: Associate Director
Clinical Sciences Division

International Centre for Diarrhoeal Disease Research, Bangladesh
CENTRE FOR HEALTH AND POPULATION RESEARCH
Mail : ICDDR,B, GPO Box 128, Dhaka-1000, Bangladesh
Phone: 880-2-8811751-60, Telex : 642486 ICDD BJ
Fax : 880-2-8823116, 8812530, 8811568, 8826050, 9885657, 8811686, 8812529
Cable : Cholera Dhaka

Memorandum

19 October 2003

To : Dr. Ali Miraj Khan
PI of research protocol # 2003-037
Clinical Sciences Division

From: David A Sack, MD
Chairman, Research Review Committee (RRC)

Sub : Approval of research protocol # 2003-037

Thank you for your memo dated 16th October 2003 with the modified version of your research protocol # 2003-037 titled "Introduction of routine zinc therapy for children with diarrhoea: safety, compliance and acceptability", which the RRC considered in its meeting held on 6th October 2003. The research protocol is approved to proceed subject to the approval of the Ethical Review Committee (ERC).

Terms of approval

The research protocol is approved as submitted for 2-year period from the date of starting the activities of the protocol. You should therefore notify the Committee Coordination Secretariat of the start date of the protocol.

This approval is only valid whilst you hold a position at the ICDDR,B; and in the event of your departure from the Centre, a new Principal Investigator will be designated for the research protocol.

This approval shall remain valid for starting the protocol for a period up to 2 years from the date of the approval of the ERC. After two years, you shall have to seek approval (revalidation) of the RRC/ERC before starting the protocol. The RRC/ERC approval shall automatically deemed to be revoked after three years if the protocol is not started.

You should notify the RRC and the ERC immediately of any serious or unexpected adverse effects on participants or unforeseen events that might affect continued acceptability of the protocol.

Any changes to the research protocol require the submission and approval of an amendment/addendum. Substantial variations may require a new protocol.

Continued approval of this protocol is dependent on your periodically updating the Centre's database for the protocol to show the progress; and a final report/completion report should be submitted at the conclusion of the protocol.

You shall submit a request for time extension of the protocol (in form) if you are unable to complete the protocol within the time mentioned in the protocol.

The RRC should be notified if the project is discontinued before the expected date of completion. The report form is available at the Committee Coordination Secretariat and on the Centre's intranet.

You are responsible for systematic storage and retention of the original data pertaining to the research protocol; and the ownership of data after certain period shall be determined as per Centre's rules and regulations.

I wish you all the success in conducting the research protocol.

Copy: Associate Director
Clinical Sciences Division

Attachment 1

Date:

(FACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator: Dr Ali Miraj Khan

Application No. 2003-037

Title of Study: Introduction of routine zinc therapy for children with diarrhoea: safety, compliance and acceptability

Trainee Investigator (if any): _____

Supporting Agency (if Non-ICDDR,B) _____

Project Status: _____

[✓] 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
   - ✓ Protocol (Required)
   - ✓ Abstract Summary (Required)
   - ✓ 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
   - ___ Informed consent form for subjects
   - ✓ Informed consent form for parent or guardian
   - ___ Procedure for maintaining confidentiality
   - ✓ 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.

Ali Miraj Khan
Principal Investigator

Trainee

RESEARCH PROTOCOL
Protocol No. 2003-037

FOR OFFICE USE ONLY		
RRC Approval:	☑ Yes / ☐ No	Date: 19.10.2003
ERC Approval:	☐ Yes / ☐ No	Date:
AEEC Approval:	☐ Yes / ☐ No	Date:

Project Title: INTRODUCTION OF ROUTINE ZINC THERAPY FOR CHILDREN WITH DIARRHEA: SAFETY, COMPLIANCE & ACCEPTABILITY

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: Zinc treatment, safety, children, acute diarrhea, compliance

Relevance of the protocol: Routine use of zinc in the treatment of acute diarrhea in children, as recommended by the Zinc Investigators' Collaborative group, is based on its proven efficacy and effectiveness in reducing the severity and duration of childhood diarrhoea (acute and persistent). The efficacy of zinc has been replicated in numerous controlled clinical trials and its effectiveness continues to be tested in several field trials throughout the world.. As zinc is scaled up as a treatment for childhood diarrhea, there will be a need for phase IV trials to identify, validate and quantify its possible side effects in relatively large patient populations. Equally important, as we plan for the actual roll-out in Bangladesh it will be critically important to have data supporting the acceptability of the dispersible zinc tablets in terms of taste and method of delivery, relative to syrup formulations already available on the market. Finally, we need to know whether or not children are receiving the zinc following discharge from hospital, for how long and what factors influence this.

Principal Investigator: Dr. Ali Miraj Khan **Division: CSD** **Phone:** 2328

Address: CSD, ICDDR,B **Email: miraj@icddrb.org**

Co-Principal Investigator(s): Dr. A.S.G. Faruque, Dr. Charles P. Larson, Dr. M.A. Salam

Co-Investigator(s): One medical officer from PSKP (to be named)

Student Investigator/Intern: None

Collaborating Institute(s): None

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

Gender
- ✓ Male
- ✓ Females

Age
- ✓ 3 months – 5 years
- ☐ 5 – 9 years
- ☐ 10 – 19 years
- ☐ 20 +
- ☐ > 65

All age groups

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

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

- [x] Dhaka Hospital
- [ ] Matlab Hospital
- [ ] Matlab HDSS area
- [ ] Matlab non-HDSS area
- [ ] Mirzapur
- [x] 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
- [x] Longitudinal Study (cohort or follow-up)
- [ ] Record Review
- [ ] Prophylactic trial
- [x] Surveillance / monitoring
- [ ] Others

Targeted Population (*Check all that apply*):

- [x] No ethnic selection (Bangladeshi)
- [ ] Bangalee
- [ ] Tribal groups
- [ ] Expatriates
- [ ] Immigrants
- [ ] Refugee

Consent Process (*Check all that apply*):

- [x] Written
- [ ] Oral
- [ ] None
- [x] Bengali language
- [ ] English language

Total sample size:

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
- [x] New treatment regime

Yes/No

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

[ ] [x] 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:

[ ] [x] a. place the subject at risk of criminal or civil liability?

[ ] [x] 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
- [x] 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: Bill & Melinda Gates Foundation

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 (S)**			
(Day, Month, Year - DD/MM/YY)	*a.* *Ist Year*	*2nd Year*	*3rd Year*	*Other years*
Beginning date: 01/11/03	*51,073*	*8,135*		
End date:	*b.* *Direct Cost :* US $44,855		*Total Cost :* US $59,208	

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.

Dr M.A. Salam

Name of the Associate Director

Signature

28/9/2003

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 Anbkhan

Date: 28.09.2003

Name of Contact Person (if applicable)

Table of Contents

☑ Check here if appendix is included

ABSTRACT SUMMARY FOR ERC

The Zinc Investigators' Collaborative group has recently recommended the routine use of zinc in the treatment of diarrhea in children. This recommendation is based on the proven efficacy and effectiveness of zinc in reducing severity and duration of childhood diarrhoera, demonstrated in numerous controlled clinical trials. The recommendation, however, also expressed the need for careful monitoring for side effects of zinc, especially unusual or excess vomiting.

The proposed study will be carried out in the Dhaka Hospital of ICDDR, B and in Dhaka community for a period of one year. The zinc therapy will be introduced as part of its standard management of children with uncomplicated diarrhoea. As zinc sulphate, 20 mg elemental zinc will be given per day for 10 days in children of either sex with diarrhea aged 3 months to 5 years which is safe and efficacious. The study will compare compliance and acceptability of the dispersible zinc tablets (which melts into a syrup when water is added) versus zinc syrup. Monitoring for adverse effects of zinc therapy will be carried out as an integral part of the routine management of a child while in hospital. Particular focus will be given to the occurrence of unusual or excess vomiting during and after hospitalization, while the child remains on zinc therapy. After discharge from hospital, caretaker of the child will be advised to report to hospital for vomiting or any other complaints which will be assessed by investigators for appropriate management.

The compliance and acceptability of the dispersible zinc tablets or syrup will be assessed in the hospital and during a follow-up home visit on day 11-12 post start of therapy. This assessment will be performed through an interview by trained research assistants/investigators that will hardly take 15 minutes. To do this, a sub-group of 1600 children will randomly be assigned to either syrup or tablet formulations, then followed to observe for differences in acceptability and compliance.

Informed written consent will be obtained from parents or authorized legal guardian of participating child after explaining the nature of the study.

This study does not involve any risk to subjects. It also will not involve any invasion of privacy or sensitive aspects of subject's behaviour or that of his or her caretaker.

All records will be maintained confidentially.

Caretaker of the child may ask the investigators any question related to study and those questions will be answered honestly.

For this study and any future use of all information they provide, subjects' anonymity will be maintained.

Parents or guardians can decide not to participate and they can withdraw at any time from the study, that will not affect usual hospital care of their child.

The results of these studies will be used in the marketing and implementation of the routine use of zinc therapy in the treatment of childhood diarrhea in Bangladesh and eventually other developing country populations. Monitoring for side effects will assist in the determination, hopefully confirmation, of zinc's safety.

Thus both patients and society will be benefited from this study.

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: Dr. Ali Miraj Khan

Project Name: : INTRODUCTION OF ROUTINE ZINC TREATMENT FOR CHILDREN WITH DIARRHEA: SAFETY, COMPLIANCE & ACCEPTABILITY

Total Budget: US $79,974 Beginning Date Nov., 2003 Ending Date: Jan., 2005

The Zinc Investigators' Collaborative group has recently recommended the routine use of zinc in the treatment of acute diarrhea in children. This recommendation is based on the proven efficacy and effectiveness of zinc in reducing severity and duration of acute childhood diarrhoera, demonstrated in numerous controlled clinical trials. The recommendation, however, also expressed the need for careful monitoring for side effects of zinc, especially unusual or excess vomiting. Thus the need for a phase IV trial as zinc is introduced into routine clinical practice, in order to assess potential side effects in a relatively large patient population. The proposed study will be carried out in the Dhaka Hospital of ICDDR,B. The zinc therapy will be introduced as part of its standard management of children with acute or persistent diarrhoea. It will be given as zinc sulphate, 20 mg elemental zinc per day for 10 days in children of either sex with diarrhea aged 3 months to 5 years.

Monitoring for adverse effects of zinc therapy will be carried out as an integral part of the routine management of a child while in hospital. Particular focus will be given to the occurrence of unusual or excess vomiting during and after hospitalization, while the child remains on zinc therapy. This will be compared with pre-zinc baseline rates of vomiting. The compliance and acceptability of the dispersible zinc tablets will be assessed in the hospital and during a follow-up home visit on day 11-12 post start of therapy. To do this, a sub-group of children will randomly be assigned to syrup and tablet formulations, then followed to observe for differences in acceptability and compliance.

The results of these studies will be used in the marketing and implementation of the routine use of zinc therapy in the treatment of acute childhood diarrhea in Bangladesh and eventually other developing country populations. Monitoring for side effects will assist in the determination, hopefully confirmation, of zinc's safety.

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

Name	Professional Discipline/ Specialty	Role in the Project
1. Dr. Ali Miraj Khan	Medicine/Paediatrics	Principal Investigator
2. Dr. A.S.G Faruque	Medicine/Public Health	Co- Principal Investigator
3. Dr. M.A. Salam	Medicine/Paediatrics	Co- Principal Investigator
4. Dr. Charles P Larson	Pediatrics/Epidemiology	Co- Principal Investigator

DESCRIPTION OF THE RESEARCH PROJECT

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.

Research Objectives:

Within the Centre's Dhaka hospital facility,

1. To monitor for adverse effects following the integration of zinc, 20 mg per day, into the Centre's routine zinc treatment protocol for children under five years of age with diarrhea.

2. To assess the acceptability of the dispersible zinc tablets in terms of taste and method of administration in hospital facility.

3. To determine zinc treatment compliance rates following release/discharge from hospital.

4. To compare rates of acceptance and compliance in children receiving zinc as syrup suspension versus dispersible tablets.

Hypothesis to be Tested:

That children (3 mo to 5 years of age) receiving zinc for the treatment of diarrhea in the tablet formulation, when compared to those receiving the syrup formulation, will demonstrate significantly different rates of acceptance and compliance.

Specific Aims:

Describe the specific aims of the proposed study. State the specific parameters, biological functions/ rates/ processes that will be assessed by specific methods **(TYPE WITHIN LIMITS).**

Specific questions to be answered:

1. Do children with diarrhea receiving zinc treatment experience excess or unusual vomiting?
2. What proportion of children refuse to take the zinc formulation and after what period of treatment?
3. Do children, post-discharge, continue to receive zinc and for what length of time?
4. Are there significant advantages to the zinc tablet or syrup formulations?
5. Do children return to the hospital because of recurrent vomiting?

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).**

Background:

Zinc plays a critical role in metallo-enzymes, poly-ribosomes, and cellular function, thus it is an essential mineral vital to human metabolism, cellular growth and immune function (1). With zinc deficiency epithelial barriers are compromised and multiple components of the immune system malfunction. The diminished immunological competence leads to an increased risk of infectious diseases and greater severity of illnesses (2). Clinical and field studies have observed an association between zinc deficiency and infectious disease morbidity (3-6). Zinc deficiency results in higher rates of infectious diseases, including skin infections, diarrhea, respiratory infections, malaria, and delayed wound healing (7). Zinc deficiency is likely to be widespread among children in developing countries along with high rates of serious infectious diseases such as diarrhea, pneumonia, and malaria (8-9). Because zinc deficiency has been associated with diarrhea and impaired immunity, recent studies have evaluated possible therapeutic or preventive roles for zinc either as a dietary supplement or as a treatment (6).

Two well-documented determinants of diarrhoeal duration are malnutrition and decreased cell-mediated immunity. A common determinant of both of these factors is zinc deficiency, thought to be prevalent in children in developing countries (10-11). The therapeutic effects of zinc during diarrhea have been investigated in several trials for acute and persistent diarrhea. These studies revealed consistent benefits of zinc(12-24). Thus far, clinical trials have found zinc supplementation or treatment to improve immune function in children in developing countries and to reduce incidence and prevalence of diarrhea as well as its duration and severity. In diarrhea, the possible mechanisms other than improvement of immune function include beneficial effects of zinc on intestinal permeability, regulation of intestinal water and electrolyte transport, brush border enzymatic function and intestinal epithelial repair resulting in reduction of stool volume and duration of diarrhea.

Zinc given as a treatment for diarrheal illness has been shown to reduce morbidity, as well as mortality. Baqui *et al* observed the lower rates of child morbidity and mortality with zinc supplementation started during diarrhoea in a large-scale community study conducted in rural area of Bangladesh, which represent substantial benefits from a simple and inexpensive intervention and remarked that it can be incorporated in existing efforts to control diarrhoeal disease (25). Thus, the use of zinc as adjunctive therapy has the potential to improve the management of diarrhea and increase survival in children, if it can be incorporated in the diarrhoeal diseases control programme in developing countries. Additional studies are being conducted in several countries of Asia, Africa and Latin America, with findings thus far indicating zinc will be beneficial in any part of the world where zinc deficiency is prevalent.

Zinc Safety:

There are varied preparations of zinc salts commercially available e.g., zinc acetate, zinc gluconate, zinc sulfate and zinc methionate. All varieties of these salts have been studied in clinical trials and major adverse effects have not been reported. In our hospital, we routinely use zinc acetate in children with persistent diarrhea and we find it acceptable by children without obvious distress. Based upon our clinical observations, vomiting is not a significant problem with zinc acetate in children with persistent diarrhea. Theoretically, toxicity of zinc due to its excess and prolonged administration includes gastrointestinal complaints such vomiting, abdominal cramp and diarrhea. Rarely, mascular incordination, hepatosplenomegally and stunted growth have been reported due to chronic exposure. None of these complications, aside from vomiting, is observed during short courses of therapy (26-28).

Acceptance and Compliance with Treatment Instructions

In an ideal world health professionals would be able to count on their treatment instructions being carried out. Such a world does not exist and we can anticipate there will be problems with adherence to the recommended 10 course of prescribed therapy. There are several explanations for this (29). At the time of discharge the child will be improving and may no longer have observable symptoms. Caretakers may conclude that the zinc therapy is no longer necessary. Furthermore, caretakers may not fully comprehend the preventive value of zinc and the relatively more complex assumptions related to secondary prevention. The child (patient) also influences compliance. If a child resists taking medication, for whatever reason, parents are more likely to stop when they perceive the grief it is causing outweighs any additional benefit. There is also the issue of provider competence in communicating instructions and the importance of full compliance. If this is not done in a caring, effective manner many parents will leave the hospital with an inadequate understanding of what is expected of them and why.

To improve the likelihood of compliance, providers will be trained to transfer a minimum, standard package of information. Following this, the provider will ask the caretaker a few key questions, thus insuring their understanding(30). Because of concerns about the "chalky" taste of the dispersible tablets and whether a sizeable proportion of children will refuse to take them, we will be comparing the tablets with an alternative syrup preparation flavored as honey.

A meeting was convened in New Delhi, India on May 7-8, 2001 to review the research findings of all the studies that investigated the role of zinc on clinical course of acute diarrhea and to draw conclusions concerning its efficacy (28). Conclusions and recommendations of the meeting were as follows:

- There is now enough evidence demonstrating the efficacy of zinc supplementation on the clinical course of acute diarrhea.
- Zinc supplementation given at a dose of 10-20mg per day for 14 days is efficacious in reducing the severity of diarrhea and duration of the episode significantly.
- However, effectiveness studies to assess different strategies for zinc supplementation to children should be taken. These studies should investigate the feasibility and sustainability of routine zinc therapy in children with diarrhea.
- Although the type of zinc salt does not seem to influence efficacy, it is important to determine the best formulation of zinc to minimize the side effects of zinc administration, essentially vomiting.

This proposal addresses the last two of these recommendations within the context of a hospital setting and post-discharge home management.

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 site : The Dhaka Hospital of ICDDR, B: Centre for Health and Population Research.

Duration: Total duration of study will be, a) 12 months of safety monitoring and b) 5 months to test acceptance and compliance. We will carry out our original study after completion of a preliminary study on pilot basis. Initially two months will be devoted for this pilot study.

Study Population:

1. Safety Monitoring: All children treated with zinc will be monitored for excess or unusual vomiting. All other unexpected events (possible side effects of zinc e.g., nausea, anorexia, abdominal cramp, metallic taste etc) though rare will be reviewed by the study's clinical researchers (AMK, ASGF, MAS).
2. Acceptance and Compliance: The hospital operates a Diarrhoeal Disease Surveillance System, which prospectively collects socio-demographic, clinical, and microbiologic information from a systematic 2% (every 50th patient) sample of patients attending this treatment facility with diarrhoeal illnesses. Children under this Surveillance System will be included in the study if they live within a 15 kilometers radius from the Centre. In addition, the next 3 living within a 15 kilometers radius admitted to the Centre will also be approached for participation in this study. This will lead to an estimated 16 children enrolled per day. These children will be randomly assigned (following consent and baseline data collection) to receive the dispersible tablet formulation or syrup formulation). We will aim to enroll 1,600 children (400 per comparison group x 2 age groups [3 to 23 months and 24 to 59 months]).

Inclusion criteria

All children with uncomplicated diarrhoea aged 3 months to 5 years attending the ICDDRB Dhaka hospital admitted to the Short Stay Ward (Rehydration Ward) or referred to the PSKP outpatient clinic will be eligible for this study. Zinc as a treatment in infants below 3 months of age has not been adequately tested (26).

Exclusion criteria

Children with co-morbidity associated with excessive vomiting. This includes whooping cough, congenital pyloric stenosis, obstructive defects of the GI tract, hiatus hernia, diabetes, uraemia, galactosemia, pylorospasm, cow's milk allergy, appendicitis, pancreatitis, and intracranial space occupying lesions. Children living beyond 15 kms from the Centre will be excluded, as will those with no address (street dwellers).

Sample size:

1. Safety monitoring: Based on the yearly patient attendance at the center, it is estimated that 60,000 children under five years having diarrhea will receive zinc therapy (20 mg elemental zinc as zinc sulphate in dispersible tablet form per day for 10 days) at the Dhaka Hospital. All instances of excess vomiting or new onset vomiting within 60 minutes following zinc ingestion will be recorded.

2. Rates of acceptance:

   a. single proportion: (level of confidence = .95)(setting d = .10)(P=0.5)

   $$N = \frac{(Z_{alpha})^2 \times (P)(1-P)}{d^2} = 96$$

   b. comparing two proportions (level of confidence = .95 and power = .80)(setting d = .10)

   $$N/gp = \frac{(Z_{alpha} + Z_{beta})^2 \times (P)(1-P)}{d^2} \times 2 = 392/gp$$

3. Compliance (mean # days):

   a. single mean: (level of confidence 0.95)(SD = 3 days)(setting d at 0.5 days)

   $$N = \frac{(Z_{alpha})^2 \times (SD)^2}{d^2} = 139$$

   b. comparison of two means(level of confidence 0.95)(SD = 3 days)(setting d at 0.5 days)

   $$N/gp = \frac{(Z_{alpha} + Z_{beta})^2 \times (SD)^2}{d^2} \times 2 = 282/gp$$

Given these estimates, we will enroll 400 children in each treatment arm. Given there may differences by age, the analysis will be stratified by age: 3 to 23 months and 24 to 59 months of age. The total number of subjects enrolled will be 1,600.

Zinc formulation

Zinc Tablets: Premix produced by Nutriset, Ltd. Premix compressed and packaged in 10 tablet blister packs by Square Pharmaceutical, Dhaka. 175,000 blister packs will be produced and sold to ICDDRB for research purposes only. The taste is somewhat chalky to adults. The tablets dissolve quickly after the addition of water, becoming a syrup.

Zinc syrup: Produced by Orion Laboratories Ltd, Dhaka. 10 mg/5 cc, to be given 10 cc per day for 10 days. 100 ml per bottle of honey tasting syrup.

Quality control of zinc formulation

We have communicated with Nutriset.They inform us that the premix is routinely checked to verify they are compressing 20 mg tablets +/- 2 mg. They have reviewed the production capacity of Square Pharmaceuticals, who also run routine checks, and have concluded they are able to maintain these

standards. The syrup is prepared by Orion Laboratories Ltd, Dhaka, Bangladesh, who also run routine quality control checks. We will obtain quality control data regularly from the companies.

Zinc therapy and randomization

Children both male and female aged 3 months to 5 years will receive 20 mg elemental zinc (as zinc sulphate) per day for 10 days (34). Following informed consent, children will be randomly assigned to tablet or syrup formulation using a blocked randomization procedure. Each block will contain a balanced 6 treatment assignments that are to be enclosed in separate envelopes attached to the consent form. Zinc will be administered under the supervision of hospital staff as long as the child remains hospitalized, ensuring adherence to the treatment schedule. After discharge from hospital, administration of the zinc treatment will be under the responsibility of the caretaker of the child. As zinc sulphate, 20 mg elemental zinc will be given as one single dose daily which is safe and efficacious. At home this single dose regimen will be continued for a total of 10 days. Before discharge from hospital, mother/caretaker will be given instructions regarding dosing and administration of zinc.

Follow up :

i) Active surveillance (limited to those in the randomized trial)

A household visit will be made once for each child after discharge from hospital. The visit will be on the 11^{th} or 12^{th} day following the start of zinc therapy. This will be done by a trained research assistant. They will be appropriately trained to identify side effects of zinc, acceptance and duration of treatment. If treatment was prematurely stopped, caretakers will be requested to explain the reason why.

ii) Passive surveillance (all patients treated over the 12 month safety observation period).

At the time of discharge from hospital, parents or guardians of children will be advised to report back to the hospital in the event of recurrent vomiting or any other possible side effect. These subjects will be assessed by one of the physician investigators.

Working definition of vomiting

It is the expulsion of contents of upper intestinal tract specially contents of stomach through oropharynx coming out mainly through mouth, in addition, occasionally through nose.

Grading of vomiting

For working purpose, we will grade vomiting as severe and nonsevere. If vomiting frequency exceeds 4 times per hour then it will be considered as severe and in such clinical situation, zinc will be stopped. Children not vomiting in the past 6 hours but vomiting within 60 minutes of receiving zinc will be observed. If it does not progress to severe grade, zinc will not be stopped.

Monitoring of zinc related side effects in the Short Stay Ward

While receiving zinc in the short stay ward (SSW) or adjacent clinic, all children will be seen by the physicians working in these sites. If in the SSW, this will be at least three times in 24 hours. In addition, nurses working in these sites continuously observe the patients for the development any unusual symptoms. For monitoring of vomiting, mothers will be provided small pieces of round metal chips to place in a box for each episode of vomiting to count frequency. On duty nursing staff and research assistants will supervise it. That will simplify the task.The hospital's current practice for assessment of the cause of excess vomiting will be followed. This includes estimation of serum electrolytes, clinical assessment for pneumonia or another focus of infection (otitis media, tonsillitis, hepatitis, meningitis) and study of the cerebrospinal fluid where clinically indicated. Management will be given according to etiology and patient will be hydrated if there is any sign of dehydration. Any other unexpected symptoms possibly attributable to zinc toxicity will be reviewed by the investigators and its management will be given accordingly.

Specific outcomes to be measured:

In children not vomiting at time of assessment (past 6 hours): All vomiting episodes occurring within 60 minutes of receiving the zinc treatment

In hospitalized children: Proportion of children with continued vomiting by presumed or confirmed etiology will be compared with vomiting in surveillance data routinely collected by the hospital prior to the onset of zinc as a treatment. This will provide prevalence of vomiting, 24 hour frequency and duration and it will also serve as baseline information.

Withdrawal from zinc supplementation

During zinc supplementation, children developing serious complications due to severe infection e.g., septicemia, pneumonia, meningitis, typhoid fever etc. zinc therapy will be stopped, because the efficacy and safety of zinc efficacy has not been tested in grave infections. In case of unusual or excess vomiting, zinc will be stopped. Such patients enrolled in the active surveillance will also be withdrawn from the study and will be considered as dropout cases. These patients will not be followed at home because they will be evaluated at hospital regarding compliance and acceptability up to the moment of withdrawal and their data will be included in the analysis. If a child develops infection of mild to moderate grade e.g., otits media, tonsillitis, shigellosis etc., during zinc supplementation, zinc will not be stopped.

Tolerance/Acceptability:

During hospitalization, research assistants will interview caretakers following the first dose of zinc (at the time of entry into the study) and once every 24 hours until discharge. Mothers will be asked whether or not their child took the zinc medication and whether, in their subjective opinion, the formulation was acceptable to their child. If reported to be unacceptable or poorly accepted, caretakers will be asked to explain. These explanations will subsequently be grouped under common themes and assessed in terms of overall compliance. Following these questions, mothers will be asked whether or not the taste or texture of the formulation is tolerated by their child. The issue here is not that it tastes "good", but that it is tolerated.

Compliance

At the time of discharge caretakers will be instructed to continue with the zinc treatment once per day until the 10^{th} day. Providers will receive a standard form outlining the specific instructions or verbal information to give and an explanation for why the child should continue for a full 10 days. Caretakers will be provided with the required number of zinc tablets. On the 11^{th} or 12^{th} day, caretakers will be visited in their homes by a research assistant. At that time the number of tablets or quantity of syrup given over what length of time will be determined. It may be difficult on the part of mother to recall. So all mothers will be provided (both for hospital & home)small pieces of round metal chips to place in a box for each day of refusal of taking zinc to count frequency of day.

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).

Treatment Center of Dhaka Hospital and adjacent PSKP outpatient clinic. Zinc tablet/ syrup will be supplied to the study patients of PSKP clinic from the protocol budget. We will include one physician of PSKP clinic to be co-investigator of our study.

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).

Zinc safety: Case by case assessment will be done and all vomiting episodes monitored. This will include prevalence of vomiting, 24 hour frequency and duration. A separate tally will be maintained of new onset vomiting episodes within 60 minutes of receiving the zinc treatment. Grading of vomiting will be recorded and the proportion of different grades will be described. Any unexpected clinical events will also be recorded and tabulated according to time of presentation following zinc intake.

Acceptance and compliance: This will include a descriptive summary of rates of refusal or reported intolerance. Both the mean number of days children receive zinc and the proportion completing a 10 day course will be described. Next these outcomes will be compared in those who received the tablet or syrup formulations. Multivariate analyses will control for co-morbidity, presence of vomiting or nausea, age of child, and other socio-demographic characteristics.

Rationale

Data from this type of phase IV evaluation is necessary for reassuring the policy makers and stake holders, manufacturers, marketing companies and distributors, and users of zinc in Bangladesh. Assessment of acceptance and compliance will assist the Centre and our zinc scaling up project partners in revising (if necessary) zinc treatment instructions and its caretaker communication messages. Acceptance of the alternative formulations will have a direct impact of SMC's business plan, the amount ordered and expected sales.

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.

The study will be conducted according to good clinical practice and the Declaration of Helsinki and relevant national guideline with the prior approval by the RRC and ERC. For those subjects enrolled in the comparative study of syrup vs. tablets, informed written consent will be obtained from parents or authorized legal guardian after explaining the nature of the study. Parents or guardians can decide not to

participate or they can withdraw at any time from the study and that will not affect usual hospital care of their child.

Steps to be followed to manage possible zinc related side effects

Monitoring at hospital : While receiving zinc, all children will be seen by the physicians at least twice in 24 hours. In addition, nurses working here will observe the patients frequently. If vomiting frequency in this study exceeds 4 times per hour then it will be considered as severe and in such clinical situation, zinc will be stopped and patient will be hydrated if there is any sign of dehydration. If vomiting frequency does not exceed 4 times per hour, zinc will not be stopped and patient will be observed for signs of dehydration. Children not vomiting in the past 6 hours but vomiting within 60 minutes of receiving zinc will be observed. If it does not progress to severe grade, zinc will not be stopped. Any other unexpected symptoms attributable to zinc toxicity will be reviewed by the investigators and its management will be given accordingly and zinc will be stopped.

In the community at home: On discharge from hospital, caretaker of the child will be advised to bring their child to the hospital for assessment by our staff if he/she vomits or develops any other symptoms or becomes worse again. After evaluating the child by our physicians, appropriate management will be given accordingly.

As zinc sulphate, 20mg elemental zinc supplementation per day for 10 days is safe and efficacious in reducing the severity of diarrhea and duration of the episode significantly. No adverse effects of zinc have been observed with this dose regimen for such a period or even with higher dose regimen in a number of clinical trials(12-24). Out of numerous clinical studies of zinc, in one study from Nepal, vomiting with zinc supplementation (as zinc gluconate) has been reported (28). From extensive literature review, it appears that there will be no or minimal risk of zinc toxicity with this dose regimen.

This study will not involve any invasion of privacy or sensitive aspects of subject's behaviour or that of his or her caretaker. Caretaker of the child may ask the investigators any question related to study and those questions will be answered honestly. All records will be maintained confidentially. For this study and any future use of all information they provide, subjects' anonymity will be maintained.

The results of these studies will be used in the marketing and implementation of the routine use of zinc therapy in the treatment of childhood diarrhea in Bangladesh and eventually other developing country populations. Monitoring for side effects will assist in the determination, hopefully confirmation, of zinc's safety.

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.

REFERENCES:

1. Aggett PJ & Comerford JG. Zinc and human health. *Nutrition Reviews* 1995 ; 53 : S16-S22.
2. Shankar AH & Prasad AS. Zinc and immune function: The biological basis of altered resistance to infection. *American Journal of Clinical Nutrition* 1998 ; 68 : 437S-463S.
3. Bahl R, Bhandari N, Hambidge KM & Bhan MK. Plasma zinc as a predictor of diarrhea and respiratory morbidity in children in an urban slum setting. *American Journal of Clinical Nutrition* 1998 ; 68 : 414S-417S.
4. Sazawal S, Jalla S, Mazumder S, Sinha A, Black RE, Bhan MK. Effect of zinc supplementation of cell-mediated immunity and lymphocyte subsets in preschool children. Indian Pediatr 1997;34:589-97.
5. Zinc and copper wastage during acute diarrhea. Nutr Rev 1990 ; 48 : 19-22.
6. Black RE . Therapeutic and preventive effects of zinc on serious childhood infectious diseases in developing countries. *American Journal of Clinical Nutrition* 1998 ; 68S : 476S-479S.
7. Prasad AS. Clinical manifestations of zinc deficiency. *Annual Review of Nutrition* 1985 ; 5 : 341-363.
8. Shrimpton R. Zinc deficiency- is it widespread but under-recognized? I: Subcommittee on Nutrition News. Vol 9, Geneva : United Nations Administrative Committee on Coordination . 1993 : 47-7.
9. Sandstead HH. Is zinc deficiency a public health problem? Nutrition 1995;11:87:92.
10. Black RE, Brown KH, Becker S. Malnutrition is a determining factor in diarrheal duration, but not incidence, among young children in a longitudinal study in rural Bangladesh. Am J Clin Nutr 1984;39:87-94.
11. Baqui AH, Sack RB, Black RE, Chowdhury HR, Yunus M, Siddique AK. Cell-mediated immune deficiency and malnutrition are independent risk factors for persistent diarrhea in Bangladesh children. Am J Clin Nutr 1993;58:543-8.

12. Sachdev HPS, Mittal NK, Mittal SK, Yadav HS. A controlled trial on utility of oral zinc supplementation in acute dehydrating diarrhea in infants. J Pediatr Gastroenterol Nutr 1988;7:877-81.

13. Sazawal S, Black RE, Bhan MK, Ghandari N, Sinha A, Jalla S. Zinc supplementation in young children with acute diarrhea in India. N Engl J Med 1995;333:839-44.

14. International Centre for Diarrhoea Disease Research, Dhaka, Bangladesh. Zinc supplementation in the treatment of childhood diarrhoea. Indian J Pediatr 1995;62:181-93.

15. Zinc Investigators' Collaborative Group. Therapeutic effects of oral zinc in acute and persistent diarrhoea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr* 2000; 72: 1516-1522

16. Sazawal S, BLack RE, Bhan MK, Jalla S, Sinha A Bhandari N. Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea - a community-based, double-blind, controlled trial. Am J Clin Nutr 1997;66:413-8.

17. Sazawal S, Black RE, Bhan MK et al. Zinc supplementation reduces the incidence of persistent diarrhea and dysentery among low socioeconomic children in India. J Nutr 1996;126:443-50.

18. Sachdev HPS, Mittal NK, Yadav HS. Oral zinc supplementation in persistent diarrhoea in infants. Ann Trop Paediatr 1990;10:63-9.

19. Roy SK, Tomkins AM, Akramuzzaman SM, et al. Randomised controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. Arch Dis Child 1997;77:196-200.

20. Roy SK, Tomkins AM, Mahalanabis D. et al. Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children. Acta Paediatr 1998;87:1235-9.

21. Faruque ASG, Mahalanabis D, Haque SS, Fuchs GJ, Habte D. Double-blind, randomized, controlled trial of zinc or vitamin A supplementation in young children with acute diarrhoea. Acta Paediatr 1999;88:154-60.

22. Bhutta ZA, Nizami SQ, Isani Z. Zinc supplementation in malnourished children with persistent diarrhea in Pakistan. Pediatrics 1999;103:1-9.

23. Hidayat A, Achadi A, Sunoto, Soedarmo SP. The effect of zinc supplementation in children under three years of age with acute diarrhea in Indonesia. Med J Indonesia 1998;7:237-41.

24. Zinc Investigators' Collaborative Group. Prevention of diarrhoea and pneumonia by zinc supplementation in children in developing countries : pooled analysis of randomised controlled trials. J Pediatr 1999; 135: 689-97.

25. Baqui AH, Black RE, El Arifeen S, Yunus M, Chakraborty J, Ahmed S, Vaughan JP. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. BMJ 2002 Nov 9;325(7372):1059.

26. Stephen S Arnon .Anaerobic Infection. *In* : Behrman RE, Kliegman RM, Arvin MA, editors. *Nelson Textbook of Paediatrics.* 16 th ed. Philadelphia: Saunders, 2000 :145.

27. *In* : Frederic D Burg,Ellen R wald, editors. Gellis & Kagan's Current Paediatric Therapy. 16 th ed. Philadelphia: Saunders, 1999:22.

28. Bahl *et al.* Effect of zinc on clinical course of acute dairrheoa. J Health Popul Nutr Dec 2001 :339-346.

29. Butler C, Rollnick S, Stott N. The practitioner, the patient and resistance to change. Compliance 1996;14(9);1357-62

30. Prochaska JO, Velicer WF, The transtheoretical model of health behavior change. Am J Health Promotion 1997;12:38-48.

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.

Dissemination

Dissemination will be ongoing and involve several strategies.

1. Dissemination manager: The zinc scale up project will provide a dissemination manager and a scale-up manager. Both are responsible for insuring the knowledge obtained from this study are applied to the scaling up exercise in Bangladesh and for dissemination locally and internationally.

2. A technical interest group including policy makers (such as GoB), representatives of the WHO and UNICEF, private laboratory (pharmaceutical industry), Social Marketing Company, clinicians, and health sector NGOs (such as BRAC) will be formed. This committee will meet prior to the start of the study, midway and at the conclusion of the study.

3. Zinc conferences: Three zinc conferences over the next 3 years will be sponsored by the project. This will include local and international experts.

4. Narrative reports will be prepared every 6 months describing the progress of this and other studies included in the scaling up project.

5. Publication of results in peer reviewed journals.

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)

This study is being planned and carried out in collaboration with the MOHFW, Social Marketing Company (Bangladesh), Nutriset, Ltd (France), USAID and WHO/Geneva.

Biography of the Investigators

Give biographical data in the following table for key personnel including the Principal Investigator. Use a photocopy of this page for each investigator.

1. Name Charles P. Larson

2 Present position Head, Health & Family Planning Systems Programme

3. Educational background: MD, MSc (Epidemiology & Biostatistics)
   Specialty Certification in Pediatrics and in Community Medicine

4. List of ongoing research protocols

   This is the first protocol I have submitted to RRC. Green banana effectiveness study concurrently under review.

5 Publications

Types of publications	Numbers
a) Original scientific papers in peer-review journals	25
b) Peer reviewed articles and book chapters	5
c) Papers in conference proceedings	>30
d) Letters, editorials, annotations, and abstracts in peer-reviewed journals	4
e) Working papers	2
f) Monographs	0

6 Five recent publications including publications relevant to the present research protocol

Asnake M, Larson, C., Teka G/E. Water handling procedures and their association with childhood diarrhea. Ethiop J Health Dev 1992;6:9-16.

Ayele F, Desta A, Larson C. The functional status of community health agents: a field trial of refresher courses and regular supervision. Health Pol Plan 1993;8:379-84.

Teferedegn B, Larson C, Carlson D. A community-based randomized trial of home made oral rehydration therapy. Intl J Epidemiol 1993;22:917-22.

Kassaye M, Larson C, Carlson D. A randomized trial of prepackaged and homemade oral rehydration therapies. Archiv Pediatr Adol Med 1994;148:1288-92.

Larson CP, Lulsegid S, Asmale T. Childhood Diarrhea, in "Ecology and Epidemiology of Health and Disease in Ethiopia", 3rd edition, in press.

1. Name : Ali Miraj Khan

2 Present position: Asst. Scientist, CSD

3. Educational background: MBBS

5. Publications

Types of publications	Numbers
a) Original scientific papers in peer-review journals	6
b) Peer reviewed articles and book chapters	2
c) Papers in conference proceedings	>20
d) Letters, editorials, annotations, and abstracts in peer-reviewed journals	3
e) Working papers	
f) Monographs	0

6 Five recent publications including publications relevant to the present research protocol

A.M. Khan, U. von Gierke, M.S. Hossain, G.J. Fuchs. Tetracycline in the treatment of cholera caused by *Vibrio cholera* O1 resistant to the drug in *vitro*. *Journal of Health, Population and Nutrition*. Volume 21 No. 1 March 2003.

Khan AM, Albert MJ, Sarker SA, Bhattacharya MK, Azad AK. Septicemia due to *Vibrio cholerae* O139 Bengal. Diagn Microbiol Infect Dis .1995 ; 22: 337-38.

Khan AM, Bhattacharya MK, Albert MJ. Neonatal diarrhoea caused by *Vibrio cholerae* O139 Bengal. Diagn Microbiol Infect Dis 1995 ; 23 :155-156.

Khan AM, Rabbani GH, Fuchs GJ. Faecal leucocytes in cholera due to *Vibrio cholerae* O139 infection. J DIARRHOEAL DIS RES 1996 Mar ; 14(1) :50-51.

A. M. Khan. G.H. Rabbani, A.S.G.Faruque. WHO ORS in the Treatment of Shigellosis. J DIARRHOEAL DIS RES 1999 June ; 17(2) :88-89.

1. Name : ASG Faruque
2 Present position: Scientist, CSD

.3. Educational background: MBBS,MPH

5. Publications

Types of publications	Numbers
a) Original scientific papers in peer-review journals	19
b) Peer reviewed articles and book chapters	4
c) Papers in conference proceedings	>12
d) Letters, editorials, annotations, and abstracts in peer-reviewed journals	3
e) Working papers	
f) Monographs	0

6 Five recent publications including publications relevant to the present research protocol

1. Faruque ASG, Mahalanabis D, Hoque SS, Fuchs GJ, Habte D. Double-blind, randomized, controlled trial of Zinc or vitamin A supplementation in young children with acute diarrhoea. Acta Paediatrica 1999; 88: 154-60.
2. Faruque ASG, Salam MA, Faruque SM, Fuchs GJ. Aetiological, clinical, and epidemiological characteristics of a seasonal peak of diarrhoea in Dhaka, Bangladesh. Scand J Infect Dis 1998; 30: 393-6.
3. Faruque ASG, Teka T, Fuchs GJ. Shigellosis in children: a clinico-epidemiological comparison between *Shigella dysenteriae type I and Shigella flexneri.* Ann Trop Pediatr 1998; 18: 197-201.
4. Faruque ASG, Hamadani JD, Hoque SS, Mahalanabis D. Picture calendar to promote Oral rehydration therapy at home for illiterate mothers: a motivational tool. J Trop Paediatr 1998; 44: 182.
5. Faruque ASG, Hoque SS, Fuchs GJ, Mahalanabis D. Randomized controlled clinical trial of rice versus glucose oral rehydration solutions in infants and young children with acute watery diarrhoea. Acta Paediatr 1997; 86: 1308-11.

Budget

Project title: Routine zinc.....
PI: Dr Ali Miraj Khan
Duration: 15 months

Name	Project position	% effort	# of post	Monthly salary	1st year	2nd year 3 mon	Total (in US $)
Dr Ali Miraj Khan (2430-7)	Principal Invest.	40%	1	1250	6,000	1,575	7,575
Dr ASG Faruque (1266-6)	Co-PI	20%	1	2055	4,932	1,295	6,227
Dr MA Salam	Co-investigator	5%	1	-	-	-	-
Dr Charles Larson	Co-investigator	10%	1	-	-	-	-
To be named	Trainee physician	100%	1	220	2,640	693	3,333
To be named	Research Asstt.	100%	4	364	17,472		17,472
To be named	Field Attendant	100%	1	265	3,180		3,180
Sub-total:					**34,224**	**3,563**	**37,787**
International Travel							
For dissemination of study findings						2,500	2,500
Sub-total:						**2,500**	**2,500**
Supplies materials							
Field supplies					1,000		1,000
~~Drug costs including Zinc~~					~~4,000~~		~~4,000~~
Sub-total:					**5,000**		**5,000**
Other Expenses							
Clinical services (Patient hospitalization Cost)					6,000		6,000
Laboratory cost (X-ray, Pathology, Bio-chemistry, Microbiology etc.)					3,000		3,000
Printing & publications					200	100	300
Sub-total:					**9,200**	**100**	**9,300**
Transportation							
Transportation cost for home visits-Dhaka					6,000		6,000
Sub-total:					**6,000**	**-**	**6,000**
Total Direct Cost					54,424	6,163	60,587
Indirect cost (32%)					17,416	1,972	19,388
Total					**71,840**	**8,135**	**79,974**

15/10/03
Md. Bozlur Rahman
Manager, Budget & Costing
ICDDR,B: Centre for
Health & Population Research
Mohakhali, Dhaka-1212

Budget Justifications (Zinc study.....)

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

1. Personnel costs reflect the actual time involvement of respective staff with the exception of Drs. Charles Larson and Mohammed Abdus Salam whose time has not been costed.

2. Drug cost: These are estimated based on actual procurement costs.

3. Laboratory costs are estimated as per ICDDR,B laboratory charge for each test (rough estimate).

4. Patient hospitalization cost: hospitalization and related (food, drugs, lab investigations) cost for patients developing adverse effects (rough estimate).

5. International travel is requested for dissemination of study findings and other study related matters.
6. Home visit cost has been estimated according to present Baby Taxi fare rate.

Study Timelines

Month	Activities	Involvement
1	Preparation for the study and training of staff	All staff
2 - 13	Actual conduct of the study and data collection	All staff
14 - 15	Analysis and manuscript writing	Investigators

CENTRE FOR HEALTH & POPULATION RESEARCH (ICDDR,B)
INTRODUCTION OF ROUTINE ZINC THERAPY FOR CHILDREN WITH DIARRHEA: COMPLIANCE AND ACCEPTANCE
BASELINE INTAKE FORM

Date ___/___/___ Interviewer # ____
d m y

1. Case ID # _____ 2. Address _____

3. # days your child has been sick? ____

4. Describe the type of diarrhea:

Watery ___ Bloody ____ Loose ____

5. What treatments have you given your child?

5.1. ORS: No ___ Yes ___
5.2. Antibiotics: No ___ Yes ___ name _____
5.3. Injection: No ___ Yes ___ name _____
5.4. other _____

6. If yes to antibiotics or other oral medications: Did your child have trouble tolerating the medication? No ___ Yes ___

If yes, did it cause vomiting? No ___ Yes ___

7. Have you ever given your child zinc? No ___
Yes, as supplement ___
Yes, as a treatment ___

8.. Marital Status:

Married, father at home ___ Married, father outside home ___

Separated or divorced _____

9. Father's education ____ 15. Father's occupation ____

10. How much do you spend on food for your household each week? _____ Tk

Thank you for answering these questions. To remind you, we will be coming to your home in about 10 days to ask you further questions. The visit can be arranged when you leave the hospital/clinic at a time and date good for you.

CENTRE FOR HEALTH & POPULATION RESEARCH (ICDDR,B)

INTRODUCTION OF ROUTINE ZINC THERAPY FOR CHILDREN WITH DIARRHEA: COMPLIANCE AND ACCEPTANCE

DISCHARGE INSTRUCTIONS

(To be read to the mother and then given to her, whether literate or not)

Your child has improved and he/she is now ready to return home with you. In spite of your child's improvement it is important to continue with the treatment instructions given to you by the hospital/clinic staff. If your child should become worse again or vomit, please return here for assessment by our staff.

You have kindly agreed to participate in a study that will allow us to compare two zinc treatments for diarrhea in children. These two choices offer exactly the same treatment, but in different forms. This treatment will help cure your child's illness, but equally important, if give it for 10 days it will lessen the chance of another illness. This does not mean your child will not become sick again, but it will be less likely.

Your child was given the zinc treatment when he/she arrived here. Now that you are returning home, it is very important that you continue to give your child the zinc treatment for a total of 10 days. Your child has received the treatment for ___ days, so that means you still have another ___ days to go.

As arranged with you, we will be visiting you in your home in ___ days. The date will be _____ and the expected time is _____. As you know, it is sometimes difficult to travel in Dhaka, so we may not arrive at the exact time scheduled.

Thank you once again for agreeing to help us with this study. We hope your child continues to improve and we look forward to meeting you again in your home.

CENTRE FOR HEALTH & POPULATION RESEARCH (ICDDR,B)

INTRODUCTION OF ROUTINE ZINC THERAPY FOR CHILDREN WITH DIARRHEA: COMPLIANCE AND ACCEPTANCE

Home Visitation Questionnaire

Date ___/___/___ Interviewer # ____
d m y

1. Case ID # _____ 2. Address _____

3. # Days since start of illness episode ___ 4. # days since discharge ____

5. Current status of child:

No further diarrhea ____ New episode of diarrhea ____

Continued diarrhea ____ Other new illness ____

6. For how many days did you give your child the zinc treatment? ____
(if 10 days, go to Q. 9)

7. For what reason(s) did you stop giving the zinc for less than 10 days

7.1. _____

7.2. _____

7.3. _____

8. What could have been done to make it more likely you gave the zinc for 10 days?

_____

_____

9. Did your child have trouble accepting the zinc? No ___ Yes ___

If yes, explain _____

_____

10. In your opinion is the taste of the medicine a problem? No ___ Yes ___

If yes, explain _____

_____

11. Why your child accepted zinc?
    Whether taste is good Yes ___ No ___

If yes, explain _____

_____

12. In your opinion did the zinc treatment make your child feel nauseous or cause additional vomiting? No ___ Yes ___

    If yes, explain _____

    _____

13. If your child becomes sick with diarrhea again, will you give your child zinc to treat the illness? No ___ Yes ___

    If no, explain _____

    _____

14. Do you wish to tell us anything further about the zinc treatment?

    _____

    _____

Thank you for answering these questions. Your participation is greatly appreciated.

CENTRE FOR HEALTH & POPULATION RESEARCH
(ICDDR,B)

INTRODUCTION OF ROUTINE ZINC THERAPY FOR CHILDREN WITH DIARRHEA: SAFETY, COMPLIANCE AND ACCEPTANCE

Voluntary Consent Form

PI : Dr. Ali Miraj Khan ICDDR,B (Phone : 8811751-60, Ext 2328) Protocol no. 2003-037.

Your child is suffering from diarrhoea. As a part of your child's routine clinical care, he/she will receive zinc (20 mg elemental zinc as zinc sulphate) once a day for 10 days. If you agree to participate in this study, your child will be randomly assigned to receive the zinc from a bottled syrup preparation or from a tablet which melts into a syrup when water is added. This will allow us to compare the acceptability of these two preparations and compliance with treatment instructions. Zinc therapy in your child will reduce the severity of the diarrhea as well as shorten its duration. Moreover, it is likely to prevent future attacks of dirrahoea. Possible side effects of zinc may be nausea and vomiting but these are not usually encountered. If it happens, we shall take appropriate steps. This evaluation of the two zinc treatments will begin with an interview in the hospital or our clinic. We will also want to interview you at your home approximately 10 days later that will hardly take 15 minutes. The exact date and time will be arranged with your permission prior to leaving the hospital. When we visit you at home you will be asked to remember how well your child tolerated the zinc treatment and for how many days it was given. We will also ask you some questions related to diarrhea of your child. After discharge from hospital if your child vomits at home or develop any new medical problem, please come back to our hospital with your kid. We will evaluate your child and management will be given accordingly.

This study does not involve any risk to your child. It also will not involve any invasion of your privacy or sensitive aspects of your behaviour or that of your child. All records will be maintained confidentially. You are always free to ask the investigators any questions you want. We will honestly answer those questions. For this study and any future use of all information you provide, your anonymity will be maintained. Your consent to allow us to interview you at hospital and at your house during follow up and to review your child's medical record is voluntary. If you should decide not to participate in this study it will in no manner affect the care your child receives. You can also withdraw at any time from the study and that will not affect the usual hospital care of your child.

If you agree to participate, please indicate this by placing your signature or your left thumb impression in the specified space below. Thank you.

Signature of the Investigator/ Representative of the Investigator	Sign... of the eyewitness	Signature/Thumb impression of mother/legal guardian
Date:	Date:	Date:

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র, বাংলাদেশ

"সম্মতি পত্র"

গবেষণার নাম ঃ বাচ্চাদের ডায়রিয়া রোগে নিয়মিত চিকিৎসার অংশ হিসাবে জিঙ্কের অর্ন্তভুক্তি এবং উহার পার্শ্ব প্রতিক্রিয়া ও গ্রহণযোগ্যতা যাচাই।

গবেষকের নাম ঃ ডঃ আলী মিরাজ খান, আই, সি, ডি, ডি, আর, বি (ফোন - ৮৮১১৭৫১ এক্সঃ- ২৩২৮), প্রটকল নংঃ ২০০৩-০৩৭

আপনার সন্তান ডায়রিয়া বা পাতলা পায়খানায় ভুগছে। ডায়রিয়া রোগে জিঙ্ক খাওয়ালে এই রোগ দ্রুত আরোগ্য লাভ করে এবং আর যাতে ডায়রিয়া না হয় তার সম্ভাবনাও থাকে। এই হাসপাতালে চিকিৎসার অংশ হিসাবে আপনার বাচ্চাকে দিনে একবার করে মোট দশ দিনের জন্য জিঙ্ক (জিঙ্ক সালফেট হিসেবে ২০ মিঃ গ্রাম ইলিমেন্টাল জিঙ্ক) সিরাপ অথবা ট্যাবলেট (যা পানিতে দিলে সংগে সংগে গলে যায়) খেতে হবে। আপনি যদি এই গবেষণায় আপনার বাচ্চার অংশগ্রহণে সম্মত থাকেন তবে আমরা বাচ্চাদের জন্য জিঙ্কের ট্যাবলেট অথবা সিরাপের গ্রহণযোগ্যতা তুলনা মূলক ভাবে বিচার করতে পারবো। হাসপাতালে আপনার অবস্থান কালে এবং আপনার বাড়ীতে (আজ থেকে দশদিন পর) যেয়ে আমরা জিজ্ঞাসাবাদের মাধ্যমে এই গ্রহণযোগ্যতা নির্ণয় করবো। তার দিনক্ষন আপনার সঙ্গে পরামর্শ করে তা ঠিক করা হবে (যা ১৫ মিনিটের বেশি সময় লাগবে না)। আমরা আপনাকে যা জিজ্ঞাসা করবো তা হলো আপনার বাচ্চা কয়দিন জিঙ্ক খেয়েছে, এবং কোন অসুবিধা হয়েছে কিনা তা সঠিকভাবে আপনাকে স্বরণ করে আমাদেরকে বলতে হবে। এ ছাড়া আপনার বাচ্চার ডায়রিয়া সংক্রান্ত কিছু তথ্য জানতে চাইবো। জিঙ্ক সেবনে পার্শ্ব প্রতিক্রিয়া হিসাবে বমি হতে পারে অথবা বমি বমি ভাব লাগতে পারে। যদিও এই ধরনের পার্শ্ব প্রতিক্রিয়া একেবারেই কম তবুও আমরা পর্যবেক্ষণ করবো এবং প্রয়োজনে উপযুক্ত ব্যবস্থা নেব। হাসপাতাল থেকে ছুটি হওয়ার পর এ ধরনের অসুবিধা হলে অথবা অন্য কোন শারীরিক অসুবিধা হলে বাচ্চাকে নিয়ে এই হাসপাতালে চলে আসবেন। সেক্ষেত্রেও আমরা উপযুক্ত ব্যবস্থা নেব।

এই গবেষণায় আপনার বাচ্চার কোন ক্ষতির সম্ভাবনা নেই। আপনার অথবা আপনার বাচ্চার গোপনীয়তা ভঙ্গ অথবা আচার আচরনের স্পর্শকাতর বিষয়ে এই গবেষণা জড়িত না। আমরা আপনার এবং আপনার বাচ্চার গবেষণা সংক্রান্ত তথ্যের গোপনীয়তা রক্ষা করবো। আপনি আমাদেরকে এই গবেষণা সংক্রান্ত যে কোন প্রশ্ন জিজ্ঞাসা করতে পারবেন এবং আমরা তার সঠিক উত্তর দেব। এই গবেষণায় আপনার বাচ্চার অংশগ্রহণের ব্যাপারে আপনি সম্পূর্ণ স্বাধীন। গবেষণায় অংশগ্রহণ না করলে এবং গবেষণা থেকে যে কোন মুর্হূতে বেরিয়ে আসলেও আপনার বাচ্চা হাসপাতালের প্রচলিত যথার্থ চিকিৎসা পাবে।

আপনি এই গবেষণায় আপনার বাচ্চার অংশগ্রহণে রাজী থাকলে নিচে আপনার নাম সই করুন অথবা বৃদ্ধ আঙ্গুঁলের ছাপ দিন। আমাদের সাথে সহযোগিতার জন্য আপনাকে ধন্যবাদ।

গবেষকের অথবা প্রতিনিধির স্বাক্ষর	সাক্ষীর স্বাক্ষর	অংশগ্রহনকারী শিশুর পিতা/মাতা/অথবা অভিভাবকের স্বাক্ষর অথবা টিপসই
তারিখ ঃ	তারিখ ঃ	তারিখ ঃ .....

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 ☑

Title: **Introduction Of Routine Zinc Treatment For Children With Diarrhea: Safety, Compliance & Acceptability**

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	%		
Adequacy of project design	%	%	
Suitability of methodology	%		
Feasibility within time period	%		
Appropriateness of budget			
Potential value of field of knowledge	%		

CONCLUSIONS

I support the application:

a) without qualification

b) with qualification ☐

- on technical grounds ☑

- on level of financial support ☐

I do not support the application ☐

Name of Referee:
Signature: _____ Date: 20-09-2003
Position:
Institution:
Address: (full postal address)

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: **Introduction Of Routine Zinc Treatment For Children With Diarrhea: Safety, Compliance & Acceptability**

PI: Scientists of ICDDRB, Bangladesh

Reviewer:

Comments :

The proposed project is of high public health interest and the results of the study should have a direct bearing on important health policy matters. The project is well written. I fully support the study. I am giving some of my comments below:

1. The investigator may consider assessing whether giving zinc during and after diarrhoea beneficially influence in preventing useless or harmful anti-diarrhoea medicines.

2. The investigators proposed to treat all children with zinc and monitor excess of unusual vomiting, it is not clear from the description whether they plan to collect baseline information on vomiting and over what period of time.

3. Under "zinc therapy and randomization" – The investigators mentioned that the children will receive "zinc acetate 20 mg/day for 10 days". They should clarify whether they mean 20 mg elemental zinc or 20 mg zinc acetate. Similarly, they state that zinc sulphate 20 mg will be given daily. Do they mean 20 mg elemental zinc as zinc sulphate or 20 mg of zinc sulphate?

RESPONSE TO COMMENTS OF REVIEWER # 1

(Project Title: INTRODUCTION OF ROUTINE ZINC THERAPY FOR CHILDREN WITH DIARRHEA: SAFETY, COMPLIANCE & ACCEPTABILITY)

1. Answer to comment # 1 : There is another protocol in our centre, approved by RRC , addressing this issue.

2. Answer to comment # 2 :

(Baseline information)

a) If a child who had not vomited in past 6 hours, vomited within 60 minutes of receiving zinc would be recorded as an adverse effect.

b) In our study, children with continued vomiting by presumed or confirmed etiology will be compared with vomiting in surveillance data routinely collected by the hospital prior to the onset of zinc as a treatment . This will include prevalence of vomiting, 24 hour frequency and duration and it will serve as baseline information. Now it has been more clearly mentioned.

2. Answer to comment # 3 : We mean 20 mg elemental zinc as zinc sulphate, now clearly stated in the protocol.

Clarson

Reviewer #2

rom: fontaineo@who.int
ent: Monday, September 29, 2003 12:25 PM
o: clarson@icddrb.org
ubject: RE: Review

nportance: High

ear Charles,

ere is the a short review of your proposal.

---

itle: Introduction of routine zinc therapy for children with diarrhoea: afety, compliance and acceptability.

his is a very well prepared proposal to assess potential side effects of inc supplementation in the course of the treatment of acute diarrhoea, and o compare the prevalence of side effects, namely vomiting, as well as dherence to treatment and acceptability between dispersible zinc tablets nd zinc syrup.

hese are important research questions that were identified as research riority issues in a meeting convened by the WHO in India in May 2001.

his proposal, which has been developed by a very experienced team of esearchers in this type of research, is perfectly adequate to answer these esearch questions, and this reviewer has no major comments/suggestions.

ust a few minor comments/clarifications:

n page 8, in the section "Zinc therapy and randomization" it is mentioned nce that the supplements are made of zinc acetate and once that they are ade of zinc suffate. I know that the zinc tablets are made of zinc sulfate. oes this mean therefore that the zinc syrup contains zinc acetate?

ne consent form should include a sentence indicating that participants can ithdraw at any time from the study.

s a detail budget was not included in the proposal sent to review, the eviewer cannot comment on it. However, a toatl budget of US$54,507 for nvestigating 1600 children with home follwo up seems quite reasonable.

---

hank you for letting me review your proposal.

nities

r O. Fontaine
edical Officer
HiLD and ADoLEsCeNT HeALtH and DeVELoPmENT
orld Health Organization

el: +41 22 791 2894
ax: +41 22 791 4853

----Original Message-----

RESPONSE TO COMMENTS OF REVIEWER # 2

(Project Title: INTRODUCTION OF ROUTINE ZINC THERAPY FOR CHILDREN WITH DIARRHEA: SAFETY, COMPLIANCE & ACCEPTABILITY)

1. Answer to comment # 1 : (Page 8) It has been corrected (as zinc sulphate)

2. Answer to comment # 2: Reviewer's suggestion has been incorporated and consent form has been revised.