

**DMONO**

Principal Investigator Dr. Ali Miraj Khan Trainee Investigator (if any) \_\_\_\_\_  
Application No. 97-016 Supporting Agency (if Non-ICDDR,B) USAID/W  
Title of Study Clinical trial to determine the efficacy and safety of hypotonic glucose based ORS. Project status:  
() New Study  
( ) Continuation with change  
( ) No change (do not fill out rest of form)

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

- Source of Population:
- (a) Ill subjects  Yes  No
  - (b) Non-ill subjects  Yes  No
  - (c) Minors or persons under guardianship  Yes  No
- Does the study involve:
- (a) Physical risks to the subjects  Yes  No
  - (b) Social Risks  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
- Does the study involve:
- (a) Use of records, (hospital, medical, death, birth or other)  Yes  No
  - (b) Use of fetal tissue or abortus  Yes  No
  - (c) Use of organs or body fluids  Yes  No
- Are subjects clearly informed about:
- (a) Nature and purposes of study  Yes  No
  - (b) Procedures to be followed including alternatives used  Yes  No
  - (c) Physical risks  Yes  No *NA*
  - (d) Sensitive questions  Yes  No *NA*
  - (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 *NA*

5. Will signed consent form be required:
- (a) From subjects  Yes  No
  - (b) From parent or guardian (if subjects are minors)  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 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. Examples 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 Cttee. for review.

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

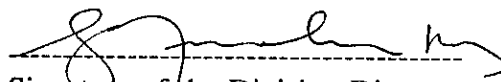
Ali Miraj Khan  
Principal Investigator

Trainee

RESEARCH PROPOSAL

SECTION I: TITLE PAGE

- a) **Title:** Clinical trial to determine the efficacy and safety of hypotonic glucose based ORS with low sodium concentration in the treatment of neonates and young infants with acute dehydrating diarrhoea.
- b) **Principal investigator(PI):** Dr. Ali Miraj Khan, MBBS  
Assistant Scientist
- Co-PI :** Dr. S.A.Sarker, MD  
Associate Scientist
- Co-investigator:** Dr. R. N. Mazumder, MBBS  
Assistant Scientist
- Consultant :** George J. Fuchs, MD  
Director, CSD
- c) **Funding Source :** USAID\W
- d) **Budget:** US \$ 66,355
- e) **Duration of the project:** One year from the date of starting
- f) **Strating date :** As early as possible
6. **SCIENTIFIC DIVISION:** This protocol has been approved by the Director of the Clinical Sciences Division.

  
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Signature of the Division Director

**Date:** 31 Aug 97 ,

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ABSTRACT SUMMARY:

This study has been designed to compare the efficacy and safety of ORS-WHO and glucose based hypotonic oral rehydration solution with low sodium content in the treatment of neonates and young infants aged up to two months with acute dehydrating diarrhoea. The osmolality of the proposed hypotonic solution will be 245 mOsmol/L where sodium concentration will be 75 mmol/l and glucose concentration will be 75 mmol/l. A total of 96 infants (only male for easy collection of urine and stool separately) with acute diarrhoea and some dehydration will be recruited for study purpose. They shall be randomly assigned to two groups. One group will get WHO-ORS and other group will get proposed hypotonic ORS solution. Patients of either group developing severe dehydration or any other major complication will receive appropriate management. On admission for each patient stool microscopy, stool culture for *Shigella*, *Salmonella*, *V. cholerae* and Elisa test for rotavirus will be done. Estimation of serum electrolytes, haematocrit, stool sodium, stool potassium, urine sodium and urine potassium will be done on admission, after 6 hours, 24 hours and 48 hours respectively. For estimation of serum electrolytes and haematocrit each time 1 ml. of blood will be taken. Patients of both groups will receive usual hospital management as practised by physicians of ICDDR,B. Total stool output, duration of diarrhoea after entry into study, change of serum sodium level, gain of body weight, intake of ORS will be considered as response variables. The study will be done in the Clinical Research & Service Centre (Dhaka) of ICDDR,B and expected to be completed by one year.

## SECTION II : RESEARCH PLAN

### A.1 HYPOTHESIS TO BE TESTED

We hypothesize that reduction of osmolality of Oral Rehydration Salt (ORS) solution will ensure safety and promote greater water absorption and thus reduce the stool volume and diarrhoeal course in neonates and young infants with acute diarrhoea.

#### A.1.1 OBJECTIVES OF THE STUDY

This protocol, we propose to carry out a randomized controlled clinical trial to evaluate clinical efficacy and safety of reduced osmolarity ORS (hypotonic ORS) solution in neonate and young infants with acute diarrhoea. The hypotonic ORS will

- reduce stool output (daily and total) and duration of diarrhoea
- reduce the need for unscheduled IV fluid
- reduce ORS intakes

#### A.1.2 BACKGROUND

The safety and efficacy of oral rehydration therapy in the treatment of dehydration due to enteric loss of fluid and electrolytes in children with diarrhoea have been recognized universally (1-3). But in neonates and very young infants the optimal sodium concentration of the oral rehydration solution has still not been elucidated (4). Only few studies have been carried out in neonates and young infants aged 1-2 months and the results have been contradictory. Pizzaro *et al* reported that neonates (aged up to 28 days) with dehydration secondary to diarrhoea can be treated successfully with oral rehydration solution recommended by WHO which has a sodium concentration of 90 mmol/l (5). But Bhargava *et al* in India have recently found a high incidence of hypernatraemia in young infants treated with this solution (6). In another study conducted in Turkey by Martin *et al*, compared the effect of rehydration solutions containing sodium 60 mmol/liter ( $K^+$  20,  $Cl^-$  45,  $HCO_3^-$  35, and glucose 125 mmol/l) in the treatment of neonates and young infants aged 1-2 months with that of older infants. From the results of that study it was concluded that neonates and young infants with infectious diarrhoea run a greater risk of developing abnormal fluid and salt retention during oral rehydration therapy because of immature renal function to excrete salt and water efficiently (7). In other studies carried out by Martin *et al*., they compared two types of ORS with sodium 90 versus 60 mmol/L (other constituents being same). They have expressed their concern that if the administration of ORS with sodium 90 mmol/L is continued after initial rehydration, diarrhoea may persist for a longer period compared to those receiving ORS with sodium 60 mmol/L because of a high stool output of sodium and fluid (4,8). There is evidence that hypotonic solutions pass through the stomach more rapidly and avidly absorbed in the proximal jejunum. In order to select logically optimal composition of ORS formulation for clinical trial, few perfusion studies; however, had been conducted with animal (25-26) and human (13,27-28) models in the recent past. One of the

major conclusions from these studies is that osmolality has a dominant role in determining the magnitude of water absorption. A substantially higher water and net sodium absorption from the solution containing sodium 60 mol/l and osmolality 220-260 osmol/l compared to solutions iso- or hypertonic with plasma has been demonstrated in those studies. The observations led the European Society of Pediatric Gastroenterology and Nutrition to recommend an ORS containing 60 mmol/l of sodium with osmolality between 200 and 250 mosmol/l for use in children in developed countries (29). The recommendation was further supported by results of a clinical trial in Finland, which has achieved favorable clinical benefit with use of a low osmolality ORS (sodium 60 m mol/l, osmolality 224 m osmol/l) in young children with acute diarrhoea (11). In this study children treated with hypotonic ORS solution had reduced frequency of diarrhoea stools and shorter average hospital stays than the group who received isotonic solution.

Based on those observations, five clinical trials with hypotonic ORS involving 734 children with diarrhoea have recently been conducted in developing countries. The results of those studies were reviewed in a Joint WHO/ICDDR, B Consultative Meeting on ORS formulation, that was held in Dhaka in December 1994 (24). Given the promising results for children with non-cholera diarrhoea, a consensus was reached during that meeting on the composition of the preferred ORS formulation for use in children. The recommended formula is (in mmol/l): glucose 75, sodium 75, potassium 20, chloride 65, citrate 10 and osmolality (in osmol/l) 245. Multi centre studies with hypotonic ORS containing the above formulation in acute diarrhoea are now ongoing. So the scope of hypotonic ORS in diarrhoea in neonate and very young children seems to be very high. Attempts should be therefore, made to identify such a solution containing low sodium content in optimizing fluid absorption, reducing stool output and diarrhoeal duration and thereby eliminating the need of free water. A clinical trial in neonates and in very young infants with diarrhoea in searching suitable ORS for clinical application is therefore, of practical importance.

### **A.1.3 SCOPE OF HYPOTONIC ORS IN ACUTE DIARRHOEA IN NEONATE AND YOUNG INFANTS**

Neonates and young infants have higher insensible water loss and lower sodium concentration in diarrhoeal stools (6). As WHO-ORS has high sodium content, there is significant risk of harmful retention of sodium in infants (less than 3 months of age) who have limited ability to excrete sodium rapidly. This make them less tolerant of a high solute load and more susceptible to salt and water retention(7,15-18). Another inconvenience related to the WHO ORS is the need of additional free water to avert the risk of hypernatremia (19) in young infants. Therefore, an additional intake of free water lead to physiological disadvantages related to exaggerated sodium secretion in the intestine (20) resulting greater stool loss. The practical limitation related to the suggestion of a free water intake may be easily misinterpreted or disregarded by the health care providers and thereby risk of developing serious electrolyte disturbances and fluid retention in neonates may be high (6, 21).

### **STUDY DESIGN**

Randomized double-blind controlled clinical trial.

#### **B.1. Sample size calculation**

Local data on clinical trial of ORS in neonates and very young infants are not available because such studies have not been carried out in our country. Data of clinical trial conducted by El-Mougi *et al* in Egypt (22) showed that in very young infants aged up to four months, outcomes of stool output g/kg (1st 6h) in Rice ORS (relatively hypotonic) group had mean 24.7 with sd. 15.0 and in conventional Glucose ORS mean 52.2 with sd. 25.3. So if we expect 30% reduction of stool output in our proposed hypotonic ORS study in comparison with what has been observed there with conventional glucose ORS and adopt the formula of

$$n = \frac{2 \text{ sd}^2}{(\text{WD})^2} \times 8 \quad (\text{Considering power } 80\% , \text{ level of significance } 0.05)$$

$$n = \frac{2 \times 25.3 \times 2}{(52.2 - 36.6)^2} \times 8 \quad (\text{sd} = \text{standard deviation})$$

wd = Worthwhile difference)

then our sample size becomes 41 in each group. Again if consider similar reduction of duration of diarrhoea in hypotonic ORS group from the same study ( duration of diarrhoea  $5.8 \pm 3.3$  and  $9.6 \pm 4.3$  h in relatively hypotonic and conventional glucose ORS Group ). So following similar formula and adopting same power and level of significance, we get here sample size of 20 patients in each group. As sample size of 41 is greater number, so we will the accept the former calculation and considering some dropouts, we will recruit 48 patients in each group, a total of 96.

## METHODS

### B.1.1 Selection of subjects

#### *Inclusion criteria:*

- Age: up to two months
- Sex: only male.
- History of acute watery diarrhea with some dehydration,
- Duration of diarrhoea less than 3 days.

#### *Exclusion criteria:*

- Severe dehydration
- Associated systemic illness, e.g., pneumonia, meningitis, septicaemia etc.
- History of intakes of antibiotic before hospitalization.
- Female (to avoid mixing of urine and stool).

The patients will be selected from OPD of Clinical Research & Service Centre of ICDDR, B. The parents or guardians will be given written and oral information regarding nature of the study and consent will be obtained before enrolment of the child into the study. This clinical trial will be conducted in the study ward of CRSC.

### B.1.2 Baseline physical examination

- identification of subject: a description of symptoms prior to entry into study
- clinical examination: both general and systemic
- anthropometric measurement
- assessment of dehydration according to recent WHO criteria

### B.1.3 Allocation to treatment group (Randomization)

After fulfillment of inclusion criteria all patients will be randomly assigned into one of the two treatment groups according to the random number table using permuted block of block length of 4, 6 and 8. One group will receive standard WHO ORS (Na<sup>+</sup> 90, K<sup>+</sup> 20, Cl- 80, Citrate 10, Glucose 111, Osmolality 311 mosmol/L) and other group will receive hypotonic ORS (Na<sup>+</sup> 75, K<sup>+</sup> 20, Cl- 65, Citrate 10, Glucose 75, Osmolality 245 mosmol/L). Number will be in sequential order and will be kept in sealed envelopes. Randomization list and sealed envelopes will be prepared by a trained and responsible person who are not involved in the study.

### B.1.4 Case- Management

After initial workup, the patient will be hydrated with assigned ORS over 6 hours. The approximate amount of ORS required in ml. will be calculated by multiplying patient's weight (in gram) times 0.075.

The breast-fed baby getting WHO ORS will be offered breast milk at least three times during this 6 hours time (i.e., at 2, 4 and 6 hours) and will continue breast feeding there after. If babies are not breast fed then plain water will be offered between 4 and 6 hours in an amount approximately one half of the volume of the ORS already ingested by the baby in addition to ORS due to be given during this period. But babies getting hypotonic ORS will not need any additional plain water during rehydration period but in case of breast-fed infants breast feeding may be permitted if the baby demands. After initial rehydration over 6 hours, weight will be taken in the same way. Then assigned ORS will be given to match ongoing stool loss only. For additional water loss (insensible loss, obligatory urine volume, sweat etc.) breast milk mostly meets this water need because solute load of breast milk is very low. So breast feeding will be allowed throughout study period. For the non breast fed baby half-diluted milk (half strength infant formula) will be offered after initial rehydration over 6 hours but milk formula will be changed to normal strength in 24 to 48 hours. Plain water will be offered 30 ml/kg divided into 3-4 times per day in non-breast-fed baby for insensible loss, obligatory urine volume, sweat etc. Any baby who develops severe dehydration due to excess vomit or noncompliance of mothers in administering ORS, will be rehydrated with intravenous conventional polyelectrolyte solution over 6 hours and then again will be assigned to scheduled ORS. Data from this patient will also be included for analysis.

The patients will be put on a cholera cot. Accurate stool output, ORS intakes, other fluid intake including plain water and urine output measurement will be done 6 hourly and body weight measurement will be taken once daily from next day onward until discharge. Stools will be measured by using a preweighed polythene container kept in a plastic bucket. Urine will be collected separately in the (PUC) urine bag to prevent mixing of urine and stool. Separated urine



will be transferred to a graduated glass cylinder for volume measurement. Vomitus will be collected in a pre weighed towel. An end of diarrhoea will be indicated by the passage of last watery stools followed by two consecutive non watery stool or absence of a stool for next 12 hours. Vital signs (pulse, respiration and temperature) monitoring will be done 8 hourly by on duty nursing staff and clinical care specially assessment of dehydration will be performed by study physician.

### **B.1.5 Laboratory investigations**

On admission (0 hour) hematocrit, serum electrolytes, stool sodium, stool potassium, urine sodium and urine potassium will be estimated and these will be repeated after 6, 24 and 48 hours. Also stool microscopy, stool culture for V. Cholera, Shigella, Salmonella and ELISA test for a rota virus will be performed on admission. For estimation of serum electrolytes and hematocrit one ml. of blood will be required each time.

#### **B.1.5.1 Illness management**

Infants who develop infection, e.g., Acute Respiratory Tract Infection (ARTI), otitis media or invasive diarrhoea will be managed with appropriate antibiotics. The study will be continued in those cases. The infants with more serious infection, e.g., septicaemia, meningitis and those developing seizure will be transferred to other ward for proper management and treatment. These infants will be withdrawn from the study but will be followed by the investigators. If diarrhoea continues beyond seven days, the infants will also be transferred to other ward for proper treatment.

### **B.2. Outcome measures**

#### **Major**

1. Total stool output (ml/kg)
2. Duration of diarrhoea (in hours) after admission.

#### **Minor**

1. Occurrence of hypernatremia or hyponatremia.
2. Total ORS intakes (ml/kg)
3. Weight gain

### **B.3 Withdrawal from the study**

Patient who will develop marked abdominal distension and paralytic ileus or any other serious complication like pneumonia, meningitis, septicaemia, marked hyponatremia or hypernatremia etc. will be withdrawn from the study and will be transferred to a special care unit for appropriate management. In case of refusal of parents to continue study with the baby will also be withdrawn from the study. However, data up to the point of withdrawal from the study will be included in the analysis. Records will be kept of their course of illness till discharge and will be evaluated at the analysis phase.

#### **B.4. Data analysis**

Data generated from the study will be entered into a microcomputer. The pre-intervention data will be summarized and compared among the groups. Continuous variable, e.g., duration of diarrhoea, total stool volume, total ORS intakes, weight gain etc. of both groups will be compared by t- test and for categorical values like occurrence of hypo or hypernatremia in both groups, a chi-square test will be used. If baseline characteristics are not similar, multi variate analysis may be applied.

Multi variate analysis may be also required if breast feeding status is found as confounding factor.

#### **B.5 Definitions**

*Stool output:* The weight of stool will be calculated in gram per kg of admission body weight expressed by time period, e.g., per hour, per 1st 6 hour, per 1st 24 hours and for the entire duration of time.

*Weight gain:* Expressed as percent increase in weight after 6 hours, after 24 hours and after diarrhoea stops compared with admission weight.

*ORS intake:* The volume of ORS taken in ml per kg of admission body weight expressed per time period, e.g., per first 6 hours, per 24 hours and for entire duration of diarrhoea.

*Hyponatremia:* Serum sodium level below 130 mmol/l.

*Hypernatremia:* Serum sodium level above 150 mmol/l.

*Watery diarrhoea:* Stool consistency is liquid and can be poured and does not contain frank mucus and blood to simulate dysenteric illness.

#### **B.6 Ethical issue:**

Clinical and laboratory monitoring of the patient's status will be done. Specially serum electrolyte status will be repeated several times and results are quickly available in our facility. Any complication developed during study, trial will be stopped and patient will be transferred to a special care unit for needful action and before enrolment in the study, the caretaker of the baby will be given full information of both types of ORS and due consent will be taken. They can refuse to participate in the study or can decide to withdraw the baby from the study. For those reasons usual treatment will not be affected. And for repeated estimation of serum electrolytes, a total of 4 ml. blood will be drawn (1 ml. each time). And that will not be harmful for the baby.

#### **B.7 Relevance of findings for policy and program formulation and decision making**

This study has been proposed to determine the efficacy of reduction of stool volume as well as duration of diarrhoea and safety of hypotonic glucose-based ORS with low sodium concentration in the treatment of neonates and young infants with acute dehydrating diarrhoea. If found superior to ORS-WHO, case management will be easier and simple for those very young infants with diarrhoea who are specially prone to develop excessive fluid and salt retention during oral

rehydration therapy. If this hypotonic ORS can reduce duration of diarrhoea then it is expected that people in the community and at household level will accept it gladly. Moreover, we will carry out the clinical trial with same formulation of hypotonic ORS with which WHO is conducting multi centre trial in developing countries both in children and adults. If all the results are favorable then there will be a single formulation of ORS which will fit everywhere. Home based dietary management cannot reduce stool volume and shorten diarrhoeal duration whereas if new ORS can do so, then it will be popularized very quickly.

## Reference

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## CONSENT FORM

(This form will be read and explained clearly in local language before consent is obtained)

Your baby is suffering from acute diarrhoea. Replacement of stool loss with rehydration solution is one of the major parts of management.

International Center for Diarrhoeal Diseases Research, Bangladesh (ICDDR, B) is planning to conduct a study in the Clinical Research Center, Dhaka to examine the effect of low salt oral saline in young infants with acute diarrhoea. We expect that this saline is better than the standard (WHO-ORS) solution and request you to allow your baby to participate in this study.

If you agree, the following procedures will be followed.

1. Your child will be kept in this center for 2-5 days or till diarrhoea stops. During this period your child will be examined daily and will be provided routine medical care.
2. During admission your child will be fed any of the two oral salines namely Standard (WHO) ORS or a glucose-based low salt ORS. Usual diet for acute diarrhoea will also be provided.
3. Stool and urine will be examined.
4. 1 milliliter of blood will be taken for Hct and serum salt at the time of admission and will be repeated at hour-6, 24 and 48 of admission.
5. The study involves no risk. We will maintain the confidentiality of the medical records.
6. At any time of the study, you may withdraw your child from the study, but his routine care by us will not be hampered. If you have any question to ask, we will be happy to answer them.
7. If you agree to participate in this study, please sign below.

\_\_\_\_\_  
Signature of  
the Investigator

\_\_\_\_\_  
Signature of witness

\_\_\_\_\_  
Signature or thumb  
impression of the  
Guardian

# BUDGET PROPOSAL

Title: Clinical trial of hypotonic ORS in neonates ...

PI: Dr Ali M. Khan

Line item	% effort	Amount in US Dollar	
		1st year	Total
<b>PERSONNEL COST</b>			
Dr. A.M. Khan, PI 29300-7-	50	6,509	6,509
Dr. R.N. Mazumder, Co-invest	20	2,682	2,682
One Res. Physician 1K. 50000 p/yr	100	2,345	2,345
Study Nurse (1) 1K. 50000 p/yr	100	1,500	1,500
Health Worker (Female) - 4 1K.	100 x 4	1,800	1,800
Secretary - Mrs. A.C. - 250	50	3,144	3,144
Statistician - H. Khatun/Alas Jafar	20	1,200	1,200
Sub-total:		19,180	19,180
<b>LOCAL TRAVEL: (Gen. trans &amp; conv.)</b>			
		500	500
<b>FOREIGN TRAVEL (For dissemination of study results in scientific seminar/conference)</b>			
		3,000	3,000
<b>SUPPLIES &amp; MATERIALS</b>			
Stationeries		500	500
Hospital/medical supplies		3,000	3,000
Nonstock others		2,000	2,000
Sub-total:		5,500	5,500
<b>OTHER CONTRACTUALS</b>			
Postage, Fax, DHL, etc.		500	500
Printing & Publication		300	300
Sub-total:		800	800
<b>INTERDEPARTMENTAL SERVICES</b>			
Transport		500	500
Medical illustration		200	200
Xerox, library service		473	473
Lab & pathological test		7,000	7,000
Patient hospitalization		10,000	10,000
Sub-total:		18,173	18,173
<b>CAPITAL EXPENDITURE</b>			
One PC with accessories for data analysis		3,500	3,500
<b>TOTAL DIRECT COST</b>			
		50,653	50,653
Overhead (31%)		15,702	15,702
<b>TOTAL PROJECT COST</b>		66,355	66,355

AK  
31/12/17



INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH  
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**MEMORANDUM**

Date : 23 January 1997  
From : Acting Director  
To : Dr. Ali Miraj Khan, CSD  
Ref : Protocol Funding

You are aware that your protocol entitled "Clinical trial to determine the efficacy and safety of hypotonic glucose based ORS with low sodium (60 mmol/l) concentration in treatment of neonates and young infants with acute dehydrating diarrhoea" was sent to USAID/W sometime ago for funding. USAID, in turn, sent your protocol to resource persons for external review.

Enclosed please find the comments of the external reviewers. Please respond to the reviewers' comments and submit your responses to Dr. Ishtiaque Zaman as soon as possible so that your responses may be forwarded to USAID for their consideration.

Thank you.

cc: Dr. George Fuchs, Division Director, CSD

Encl: As stated.



GUIDE FOR EVALUATING USAID/CHR PROPOSALS

**Name of proposal:** Clinical trial to determine the efficacy and safety of hypotonic glucose based ORS with low sodium (60 mmol/l) concentration in the treatment of neonates and young infants with acute dehydrating diarrhoea.

**Name of proposed investigator:** Dr. Ali Miraj Khan MBBS  
Assistant Scientist

1) **Goals:** The goal of the study, as summarized in the title, is appropriate.

2) **Design:**

*Definitions:* Mostly well-described and appropriate. The one omission, that may have been overlooked, is whether the study will be double-blinded? Certainly, the study should be double-blinded. The investigators should clarify this point.

*Sample size and strategy:* Well-described and appropriate

*Analysis Plan:* A bit weak, but acceptable.

*Feasibility:* High. ICDDR,B is optimal site to do study.

*Methods:* Well-described and appropriate.

3) **Appropriateness:**

Optimizing the formulation of ORS has high potential for improving child survival in this very high risk age group

4) **Timing and budget:** Acceptable.

5) **Ethics:** Acceptable.

6) **Background:** Acceptable

7) **Other:** None

4. CLINICAL TRIAL TO DETERMINE THE EFFICACY AND SAFETY OF HYPOTONIC GLUCOSE-BASED O.R.S. WITH LOW SODIUM (60 MMOL/L) CONCENTRATION IN THE TREATMENT OF NEONATES/YOUNG INFANTS WITH ACUTE DEHYDRATING DIARRHOEA

Proposed investigators: Khan, Mazumder & Fuchs

1. Goals

The research has the clear primary goal of comparing the efficacy and safety of hypotonic, low sodium ORS solution with WHO ORS solution in neonates/very young infants.

2. Design

The study adopts the standard design for clinical trials. The investigators may like to consider the possibility of a factorial design with four treatment arms, viz. i) standard WHO solution (high sodium isotonic), ii) low sodium isotonic solution, iii) high sodium hypotonic solution, iv) low sodium hypotonic solution. This design may be more informative than the simple two-arm trial.

The investigators should explain why 2 months has been chosen as the age cut off for the trial. A definition of 'watery' diarrhoea should be provided.

The sample size calculations are adequate. The source of the formula should be indicated. If the four-arm trial suggested above is adopted, additional sample size allowance would need to be made for formal testing of the interaction between sodium concentration and osmolarity (see any standard textbook on clinical trials). The exact procedure by which eligible infants would be 'selected' for the trial should be described. The inclusion of both breastfeeding and non-breastfeeding infants in the trial adds considerable complexity to the study design. Since non-breastfeeding two-month old infants are presumably very rare in the Bangladeshi context, the

investigators might like to restrict the trial to those still breastfeeding. Alternatively, the randomization could be stratified to include both breastfed and non-breastfed infants in separate strata, but this would involve doubling the sample size.

The analysis plans are entirely non-specific and uninformative. At the very least, they should state which outcomes measures will be analyzed using which techniques. The analysis plan must take into account the fact that with such a small sample size, treatment groups may not be similar in baseline characteristics (disease severity, nutritional status etc.), even with randomization. Multivariate analyses that take into account baseline characteristics may be required.

Feasibility - see comments on breastfeeding. No forms or record abstract provided.

### 3. Appropriateness

One of the main criticisms of ORS has been that it does not satisfy mothers because it does not curtail purging. Any reformulation that would reduce stool output, and also reduce the risk of side effects, would therefore be an important improvement. Since young infants have the highest risk of dehydration during episodes of acute diarrhoea, interventions focused on this age group are particularly welcome.

This study appears to be breaking new ground in directly comparing a low sodium, hypotonic solution with standard WHO solution in this age group. Its significance would be enhanced by adopting a factorial design, since the design as stands will not allow any conclusions to be drawn about whether it is the low sodium concentration that is important, the low osmolarity, or the combination of the two.

### 4. Timing & Budget

Insufficient information provided to evaluate this component.

### 5. Ethics

The investigators state that they will evaluate serum electrolytes, but do not state i) whether these results can be made available quickly enough for the individual child with signs of hypo/hypernatraemia to be immediately discontinued from the trial, or ii) whether the incidence of hypo/hypernatraemia will be continuously monitored by an independent monitor with the power to stop the trial if the magnitude of these effects should become unacceptable.

### 6. Background

The investigators should consult a standard textbook on clinical trials for information on factorial designs and stopping rules.

**Name of proposal:** Clinical trial to determine the efficacy and safety of hypotonic glucose based ORS with low sodium (60 mmol/l) concentration in the treatment of neonates and young infants with acute dehydrating diarrhoea (4)

**Name of investigator:** Khan et al.

**Date of review:** December 1996

### Comments

*Literature review:* Should mention the results of 5 clinical trials with hypotonic ORS (total of 734 children) that were conducted in developing countries and were reviewed in 1994.

*Sample size calculations:* Sample size calculations are based only on one response variable (total stool output). They should be done also on the second response variable mentioned (duration of diarrhea).

*Methodology and analysis:* Breastfeeding status may be a confounding factor in this study and should be carefully controlled for in the analysis. Thus, the analysis should include multivariate analyses to control for this variable.

*Ethical issues:* should be discussed.

*Significance of the study:* This section does not address the main issue related to the use of ORS: its distribution and use at the community and household level. While it may be true that a specific formula for neonates is preferable clinically for treatment in hospital settings, the introduction of more than one type of ORS at the community and household level greatly complicates its use and may have a negative effect on its acceptability. This should be discussed. The proposal should also discuss the hypothesized benefits of ORS, compared to home-based dietary management of diarrhea.

**Response to the previous proposal entitled “Clinical trial to determine the efficacy and safety of hypotonic glucose based ORS with low sodium (60 mmol/l) concentration in the treatment of neonates and young infants with acute dehydrating diarrhoea”**

#### **Responses to the comments of 1st Reviewer**

- 1) **Goals:** We appreciate the comment.
- 2) **Design:** The study is double blinded and the proposal has been revised accordingly.

We appreciate the reviewer’s comments on sample size.

#### **Analysis plan**

We incorporated multivariate analysis to adjust breast feeding as confounder in data analysis of the revised version (Section B.4).

We appreciate the comment on Feasibility, Methods, appropriateness, timing, ethics and background.

## Responses to the comments of the 2nd reviewer :

1. Comments on the goal are appreciated:
2. Design: We appreciate the reviewer's suggestion that a 4 arm trial could be more informative. However, our study subjects are neonates and infants up to 2 months. These young children are known to have relatively immature renal function and difficulty in handling high sodium load. It has been shown from clinical studies that high sodium induces retention of fluid volume in young infants. Mucosal injury is quite common in infants with infectious diarrhoea and there is concern that accompanying impaired glucose absorption results in osmotic diarrhoea, an increase of glucose with lower sodium to make it isotonic solution may result in osmotic diarrhoea in this particular group of subjects. The scientific basis for hypoosmolar solutions derives from latest 3 studies (Sandhu *et al* 1989, Elliot *et al* 1989, Farthing *et al* 1989). From those studies, it was concluded that optimal water absorption can be obtained by using hypotonic solution with glucose concentration of 50-100 mmol/l. We have planned our formulation of ORS on this basis and which also is identical to the hypotonic reformulation currently under study by WHO. Though we appreciate the reviewer's idea of a 4 arm trial, we believe that first phase of hypotonic ORS trial in neonates and very young infants should be on possible safe side. Therefore, we feel a 2 arm trial with WHO-ORS and hypotonic ORS in those particular group of patients would be more appropriate.

### Cut-off point

As physiological maturity of renal function is usually achieved after two months, we have chosen this age as the cut off for the trial.

### Definition of watery diarrhoea

Definition has been incorporated in the revised version in section B.5.

### Sample size

We appreciate the comment. Source of formula for the sample size calculation has been mentioned in section B.1 of the revised version.

### Selection of infants

The exact procedure by which eligible infants will be selected has been described under different headings e.g., inclusion criteria, exclusion criteria, enrolment of subjects, base line physical examination and randomization.

### Breast feeding

We agree with the suggestion of reviewer and therefore will restrict the trial to those still breast feeding to avoid unnecessary complexity of study design. If not possible, then multi variate analysis will also be applied to adjust breast feeding as a confounder.

### The analysis plans

Analysis plans have been revised in Section B.4. Continuous variables e.g., duration of diarrhoea, total stool volume, total ORS intake, weight gain etc. of both groups will be compared by t-test and for categorical values e.g., occurrence of hyp- or hypernatremia in both groups chi-square test will be used. If baseline characteristics are not similar, multi variate analysis may be applied.

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**27 NOV 2004**

**Record abstract**

Record abstract has been added.

**Appropriateness**

We appreciate the comment but considering physiological aspect of very young subjects specially immaturity of renal function, we are not doing a factorial design with a 4 treatment arm.

**4. Timing & Budget**

Has been elaborated in the revised version.

**5. Ethics**

In our facility, results of serum electrolytes are quickly available. Furthermore, any individual child with sign of hyponatremia or hypernatremia, will be withdrawn from the study immediately and appropriate measures will be taken.

**6. Background**

For reasons as mentioned above we will not adopt a factorial design in the proposal.



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**Responses to the comments of 3rd Reviewer:****Comments:****Literature review:**

The results on 5 previous clinical trials with hypotonic ORS in developing countries were reviewed by WHO/ICDDR,B Consultative meeting in 1994 and were found promising. The literature has been referenced in the background of the proposal ( ) of the revised version.

**Sample size calculations:**

We accept the suggestion. The sample size calculation has also been done also on the second response variable (duration of diarrhoea) and has been incorporated in Section B.1 of the revised version.

**Methodology and analysis:**

We incorporated the suggestion regarding multi variate analysis in Section B.4.

**Ethical issue :**

The patients will be monitored carefully by clinical examination and by thorough laboratory investigations. The parents will be given full information about the nature and the type of the study. Informed consent will be obtained from parents before enrolling the patients into the study. The parents are at liberty to withdraw their consent at any time during the study. In such cases, usual treatment will not be affected. This issue has been addressed in Section B.6. Obtaining permission to perform the study from the local Ethical Review Committee is under process.

**Significance of the study:**

If this hypotonic ORS reduces duration of diarrhoea as well as total stool volume and proves to have less side effects then it is expected to have significant implications to improve management of diarrhoea in neonate and very young infants. Therefore we believe that the findings of the study will provide substantial contribution in formulating improved ORS for wide use in clinical as well as community setting.