Attachment 1. (FACE SHEET) ETHICAL REVIEW COMMITTEE, ~~ICDDR,B~~ Library Date 7/2/95

Principal Investigator Dr. R.N. Mazumder Trainee Investigator (if any) _____

Application No. 95-004 Supporting Agency (if Non-ICDDR,B) _____

Title of Study: Estimation of absorption of electrolytes ... in children with acute diarrhoea.

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).

1. Source of Population:
   (a) Ill subjects (Yes) No
   (b) Non-ill subjects Yes (No)
   (c) Minors or persons under guardianship (Yes) No
2. 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)
3. 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
4. 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)
   (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 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.

R.N. Mazumder
Principal Investigator

Trainee

ENTERED 2 1 JUN 1995

RESEARCH PROTOCOL

1.	Project Title:	Estimation of absorption of electrolytes and macronutrient between reduced osmolar oral rehydration solutions in children with acute diarrhoea
2.	Principal Investigator: Co-Principal Investigator:	Dr. Ramendra N. Mazumder, Dr. Mihir K. Bhattacharya
3.	Co-Investigators:	Ms. Makduma Khatoon, and Dr. Ali M. Khan
4.	Consultants:	Dr. Dilip Mahalanabis, and Dr. George J Fuchs
5.	Proposed starting date:	When protocol is granted
6.	Proposed duration:	Twelve months
7.	Budget Total:	US $ 75,472.00
8.	Donar Agency:	UNICEF (probable)
9.	Approval:	This protocol has been approved by the Clinical Sciences Division (CSD)

Signature
Acting Divisional Director, CSD

Date : 7/2/95

10. Abstract Summary

Recent results of the animal experiments with secretory diarrhoea suggest that reduced osmolar oral rehydration solution results in increased net sodium and water absorption. Clinical study with acute diarrhoea also shows therapeutic efficacy of reduced osmolar solutions over hyper osmolar solutions in reducing stool frequency and duration of hospitalization in children. However, the question of absorption of electrolytes (Sodium, Potassium, Chloride and Total carbon dioxide) and glucose /carbohydrate (rice) from reduced osmolar solutions needs to be answered in children with acute watery diarrhoea. In a metabolic balance study, the present proposal aims to measure the net absorption of electrolytes and macronutrient from three oral rehydration solutions: (1) reduced osmolar rice-based ORS (Na^+: 75 mmol/L; Cl^-: 65 mmol/L; K^+: 20 mmol/L; Citrate: 10 mmol/L; and Rice powder: 35 g/L); (2) reduced osmolar glucose-based ORS (Na^+: 75 mmol/L; Cl^-: 65 mmol/L; K^+: 20 mmol/L; Citrate: 10 mmol/L; and glucose: 75 g/L) and (3) standard WHO/UNICEF ORS (Na+: 90 mmol/L; Cl^-: 80 mmol/L; K^+: 20 mmol/L; Citrate: 10 mmol/L; and glucose: 111 mmol/L). Children suffering from acute watery diarrhoea of not more than 72 hours with clinically evident dehydration will be studied. Patients with severe dehydration will be partially rehydrated with intravenous acetate solution (Na^+: 133 mmol/L; CL^-: 98 mmol/L; K^+: 13 mmol/L and HCO_3^-: 48 mmol/L) within 4 hours. Subjects will be randomly assigned to one of the oral rehydration solutions. Metabolic balance will start from the beginning of rehydration for patients with some dehydration. For severely dehydrated children study will begin after partial correction of dehydration. The study will be continued for following 48 hours. All intakes and output (ORS, plain water, food, stool, urine and vomitus) will be meticulously measured and used to estimate the absorption and loss during the study period. *Vibrio cholerae* positive cases will be treated with oral erythromycin. Food will be offered to the children after initial correction of dehydration. Subjects will be admitted in the metabolic ward and will be under constant medical supervision. The patients will be discharged after the end of diarrhoea and when justified by clinical evaluation. All medical records will be kept confidential and will remain with the investigator.

Reviews:

(a) Research Review Committee_____

(b) Ethical Review Committee_____

RESEARCH PLAN

A. INTRODUCTION

A.1 Objective

(1) Electrolytes are better absorbed from reduced osmolar solutions in acute diarrhoea;
(2) Macronutrients are efficiently absorbed from reduced osmolar oral rehydration solutions in children;

A.2 Background

Since the recommendation of salts-glucose-water solution (ORS) as oral rehydration therapy in the treatment of diarrhoea (Darrow *et al.*, 1949; Chattergee *et al.*, 1953 and Harrison *et al.*, 1954), oral rehydration solution has been identified as a unique tool to combat dehydration and is saving millions of lives (UNICEF Report, 1986). Glucose-linked enhanced absorption of sodium and water from the small intestine remains largely intact during acute diarrhoea of diverse etiology and is the basis of glucose based oral rehydration solution. However, it has been observed that presently used glucose-based oral rehydration solution neither reduces stool volume nor duration of diarrhoea in children under five years of age with rota virus diarrhoea and cholera (Mahalanabis *et al.*, 1974; Sack *et al.*, 1978 and saberi *et al.*, 1983). In adults with secretory diarrhoea caused by cholera, diarrhoeal stool output may increase by 15-20% when treated with ORS (Pierce *et al.*, 1969). WHO ORS contains 20 g of glucose which in 2-4% clinically dehydrated children with acute diarrhoea, may exceed the capacity of sick intestine to absorb it; in such case ORS containing 20 g of glucose may worsen the diarrhoea (Hirschhorn *et al.*, 1980).

Reduced osmolar oral rehydration solution in the management of diarrhoea : presently used glucose based ORS has a relatively high concentration of sodium (90 mmol/l) and is hyperosmolar (311 mOsmol/l) in respect to human plasma. Hyper osmolarity with a high concentration of glucose is an important limiting factor for efficient absorption of WHO ORS. It has been speculated that in acute infective diarrhoea glucose is not completely absorbed from the small intestine (and enter into to the colon) which may be responsible for osmotic diarrhoea (Saberi *et al.*, 1983). Recent clinical studies suggest that stool volume, and thus water loss may be reduced if glucose is replaced by rice-based polymeric substrate that reduces osmolarity (Patra *et al*, 1982 Molla *et al*, 1985). Therefore, it is possible that reduced osmolar monomeric glucose-based solutions may reduce stools volume.

Although the central role of glucose sodium co-transport in oral rehydration therapy is unquestioned, the optimal composition of ORS as to glucose concentration and osmolarity, has not been clearly established. To select logically optimal composition of ORS formulations, few studies have been performed in animal models (Wapnir *et al.*, 1985; Lifshtz *et al.*, 1985 and Rolston *et al.*, 1987) and in human models (Elliot *et al.*, 1989; Sandu *et al.*, 1989 and Hunt *et al.*, 1992). One major conclusion from

these studies is that solute load and concentration are important in determining the absorption of water; reduced osmolar ORS induces greater water absorption than iso- or hypertonic ORS. These observations provoked further studies with a human model of secretory diarrhoea with the cholera toxin to assess water and solute absorption from ORS with osmolality of 311 mOsmol/l and that with 220 mOsml/l in jejunum (Hunt *et al.*, 1994). Results were consistent with earlier studies showing greater water and sodium absorption from reduced osmolar ORS compared to hyperosmolar ORS. Recently, a clinical trial has compared a glucose-based reduced osmolar ORS with WHO ORS in the treatment of acute diarrhoea in Finish children (Rautanen *et al.*, 93); reduced osmolarity ORS was associated with less stool frequency and early recovery, and thus strongly supports the conclusions drawn from earlier animal and human perfusion studies. However, this study did not measure the stool output, and no balance study has yet been conducted to explain the total gut handing of reduced osmolar solutions in children with acute diarrhoea.

If reduced osmolar oral rehydration solution is effective in maintaining hydration, it would also make positive electrolyte balance and carbohydrates (glucose or starch) in acute diarrhoea. We propose to conduct a balance study to estimate and compare the absorption of electrolytes and carbohydrates between reduced osmolar oral rehydration solutions and standard glucose-based electrolyte solutions in acute watery diarrhoea in children. We wish to test our hypothesis that osmotic penalty is curtailed when reduced osmolar solutions are used in the management of diarrhoea.

B: Specific aims

(1) Estimation of absorption of Na^+, Cl^-, K^+, and Total CO_2 from two new formulations of ORS and standard WHO/UNICEF ORS in the children with acute diarrhoea;

(2) Estimation of absorption of Rice powder or Glucose from three oral rehydration solutions;

(3) To compare the absorption of electrolytes and carbohydrates/glucose among three ORS;

(4) To compare the absorption of electrolytes and carbohydrates/glucose between reduced osmolar glucose-based ORS and reduced osmolar rice-based ORS;

C: Response variables

The **primary response** variables of the study are:

- co-efficient of absorption of total Na^+, K^+, Cl^- and total CO_2 from the time of start of ORS and for first 48;
- co-efficient of absorption of carbohydrate;

Secondary response variables are as follows:

- total stool output, in g/kg of body weight, from the time of initiation of ORS solution until end of diarrhoea;
- duration of diarrhoea, in hours, after randomization and initiation of treatment with the formulation;
- rate of stool output, in g/kg/h, during first 24 hours of initiation of the ORS;
- intake of ORS and plain water, in ml/kg of body weight, from initiation ORS until diarrhoea stops;
- urine output, in ml/kg of body weight;
- weight gain, percent increase in body weight, after cessation of diarrhoea compared to admission body weight;

D.1 Study design

D.1.1 Inclusion criteria: subjects and methods

- Age: 6 mo-7 years;
- Sex: Only male children will be included in the study for better separation and collection of stool and urine;
- Patients who have had diarrhoea for < 72 hours prior to admission, and three or more watery or liquid stools in the last 24 hours;
- Clinically evident dehydration;

D.1.2 Exclusion criteria

- Patients with a serious concurrent illness such as meningitis or pneumonia, or with a recognized chronic disease will not be included;
- Weight for height < 40% of NCHS median;
- Antibiotic therapy within three days prior to admission;
- History of diarrhoeal illness within two weeks before admission (to avoid cases with prolong diarrhoea);
- History of passing blood or blood and mucous in stool;
- Patients with pedal oedema (kwashiorkor);

D.2 Sample size estimation

As this is a metabolic balance study to determine the absorption of electrolytes and carbohydrates, ten subjects will be enrolled in each sub group. Therefore, a total of sixty subjects will be studied in each group (explained in randomization section).

D.3 Enrolment of subject

D.3.1 Informed consent

Since the study subjects will be minor, written informed consent for participation of the children in the study will be required from either of the parents, or of their legal guardians. Parents or guardians will retain the right to withdraw their children from the study at any stage of the disease without affecting further care of the patient.

D.3.2 Baseline examination

After assessment of eligibility and obtaining informed consent, patients will be admitted in the metabolic ward of the Clinical Research and Service Centre of ICDDR, B. Medical history of the children will be obtained from their parents, or legal guardians for information such as duration diarrhoea , stool frequency, stool character, any administration of ORS or intravenous fluid or any treatment given prior to admission. A thorough physical examination including vital signs (rectal temperature, pulse, respiratory rates and blood pressure), dehydration status (following WHO guidelines) and admission body weight (dehydrated body weight) will be done by one the investigators. All information will be recorded in predesigned form.

The following laboratory investigations will then be performed on the children before their allocation to different groups.

- **Stool**: determination of electrolytes, mmol/L; osmolarity, mOsmol/L and co-efficient of absorption carbohydrate, %; dark-field examination for demonstration of *V. cholerae;* and culture (to identify enteric bacterial pathogen); ELISA test for rota virus.
- **Blood**: two (2.0) ml. of venous blood will be drawn for determination of electrolytes (mmol/L), osmolarity (mOsmol/l), TC, DC, Hct, and Sp.gr.
- **Urine**: electrolytes (mmol/L) and osmolarity (mOsmol/L).

D.3.3 Allocation to the treatment group (randomization)

Subject's stool will be tested for rota virus; on the basis of this test subjects will be divided into two groups: rota virus positive and rota virus negative. In each group, children will be assigned consecutive numbers with type of ORS. Assignments will be done using a table of random numbers, using block randomization method of variable block lengths such as 4, 8, and 12. Randomization list will be prepared by a responsible and appropriately trained who is not otherwise involved with the study.

D.4 Standard case management

- **correction of dehydration:** on completion of baseline examination and collection of samples, patients will be rehydrated with intravenous acetate solution (Na^+: 133 mmol/L; CL^-: 98 mmol/L; K^+: 13 mmol/L and HCO_3^-: 48 mmol/L). Children with severe dehydration will be hydrated with 30-40 ml/kg of acetate to restore normal blood pressure and adequate circulating blood volume as evidenced by a good volume radial pulse. volume of intravenous fluid administered for initial hydration will be recorded. If a patient fails to achieve adequate hydration within 4 hours will not be included in the study.

- **maintenance phase (beginning of the study)**: time of randomization to the study groups will be after partial correction of dehydration for severely dehydrated patients; children with some dehydration will be randomized directly and assigned ORS will be offered with a marker. From the time appearance of the first marker or **0** h, all intake of fluids, food, and all output including stool, urine and vomitus will be meticulously recorded by trained persons for following 48

hours. Measured amounts of assigned ORS (Table 1) in bottles of 500 ml will be provided to every study patient; cup and spoon will also be supplied to facilitate measured intake. Patients or attendants will be instructed on administration of ORS. From time **0** h , loss of fluid in stools and vomitus will be replaced on weight for weight basis.

- **supplemental intravenous fluid therapy:** if signs of dehydration appear after initial hydration or fails to maintain hydration because of severe purging and or vomiting, patients will reweighed and vital signs will be recorded. Rehydration will be done with intravenous acetate solution according to WHO criteria and also in consideration with the fall of body weight.

- **Plain water:** Water will be offered during maintenance phase and record will be maintained.

- **feeding:** children will receive defined hospital diet appropriate for age after correction of dehydration. Breast fed babies will continue breast milk *ad libitum*.

- **antibiotics:** children with cholera (determined by dark field examination of stool immediately or by stool culture) will be treated with erythromycin, 12.5 mg/kg every 6 hours for 72 hours (12 doses). Dose will be repeated if one vomits within 15 minutes of administration of the drug.

- **investigations:** fecal culture will be repeated daily if an enteric pathogen is isolated from admission sample; Re-determination of electrolytes, hematocrit and serum specific gravity at 24 hours and at 48 hours of the study.

D.5 Withdrawal from the study: If any patient leaves the hospital before completion of the study or if a patient requires unscheduled treatment for an intercurrent illness will be considered as non-compliance of the subject to the study and data up to the time of withdrawal will be included in the analysis.

E.1 Organization of the trial

E.1.1 Description of the facilities and patient population

Clinical Research and Service Centre, Dhaka, of the International Centre for Diarrhoeal Diseases Research, Bangladesh (ICDDR,B) provides care and service to ≈ 100,000 patients annually for diarrhoea related diseases. Children who attend the Clinical Research and Service Centre, Dhaka, of the ICDDR,B for treatment of their acute diarrhoeal problem will form the study population.

E.1.2 Methods

- body weight: children will be weighed by an electronic balance (Sartorius);
- stool will be collected in a bucket placed underneath the "Cholera cots" and volume will be measured (in ml and g) by measuring cylinders with a precision

of 1 ml and will also be weighted in a electronic balance (Sartorius);

- urine volume (ml): urine will be collected in "Paediatric Urine Collector (PUC)" bags and will be measured in measuring cylinders.
- vomitus (g): a pre-weight bowl will be provided for collection of vomitus. If a patient vomits on the floor or on the cot, that will be mopped using pre-weighed napkins and the weight of the vomitus will be determined by deducting the dry weight of the napkins from their wet weights immediately after mopping.
- electrolyte (mmol/L) and osmolarity (mOsmol/L) of stool, ORS, fluid, vomitus and urine will be measured Beckman auto analyzer. Energy of all intake and output will be determined by adiabatic bomb calorimetry; nitrogen concentration will be estimated by Kjeldahl method and fat will be estimated by the method of Van De Kamer et al. Carbohydrate will be estimated by calculation.
- recording vital signs: every 4 hours starting from time "**0**" until discharge of the patients.
- physical examination: at time "**0**" and at 24 hourly intervals throughout the entire period of hospitalization, at the time of administration of supplemental intravenous fluid therapy.
- samples: all intake and output samples will be assayed immediately if possible; if not all intake and output samples will be stored at -40°C until assay.

F. Definitions:

- **duration of diarrhoea after admission:** interval (in hours) between time "**0**" until passage of last liquid or semi-liquid stool prior to two formed stools or prior to 12 hours during which no stool passed.
- **stool output:** volume and weight of watery stools from time "**0**" until cessation of diarrhoea, measured to the nearest 1 ml. and 1 mg.
- **ORS and plain water intake:** the volume of ORS or plain water taken in ml/kg of admission body weight expressed after first 24 hour and for the entire duration of diarrhoea.
- **weight gain (or loss):** the increase (or loss) in weight after 24 hours and after recovery compared with weight on admission and expressed as a percent of admission weight.

G. Analysis of data

For normally distributed continuous variables ANOVA will be performed for comparison among study groups and student's t test for comparison between two groups. A non-parametric tests will be applied for data that are not normally distributed. Proportions will be compared using the Chi square tests, and Fisher's exact test when expected cell size in any of the group is ≤ 5. The followings will be compared:

G.1 Pre-treatment data

Analyses of the followings will be done to determine pre-intervention comparability: age in months, duration of diarrhoea in hours, admission and rehydration weights, degree of dehydration on admission, proportion of children with different etiologic

diarrhoea, the amount of ORS solution and other fluids, and intravenous fluids received before entry into study.

G.2 Post-treatment data

Other than the response variables mentioned above, the following clinical and laboratory data will be analyzed: electrolytes of ORS, food, at **0 h** and stool, urine, vomitus at **48 h** of the study; co-efficient of absorption will be calculated as standard formula. stool volume during rehydration period (as ml./kg of rehydration weight); hematocrit, serum specific gravity and the frequency and the amounts of unscheduled intravenous fluid, and number with supplemental intravenous fluids.

H. Significance of the study

The results of this study would be useful to determine the net absorption of sodium and water among three different oral rehydration solutions. Based on the absorption efficiency, it would be possible to identify one the three ORS for the treatment of diarrhoea. The results of this *in vivo* study with young children will help future formulation of an ORS for efficient absorption of electrolytes and carbohydrate (polymeric or monomeric) which may shorten duration of diarrhoea (which is a concern among users) and/or reduce volume of stool, that would greatly help in promotion of ORT and in the management of diarrhoeal diseases.

ABSTRACT SUMMARY FOR THE ETHICAL REVIEW COMMITTEE

1. Requirement of Study Population

This study will require children, aged 6mo-7 years with acute diarrhoea of ≤72 hours duration and signs of some, or severe dehydration. A total of 60 children will be required to be studded in 3 groups, and in order to get this many evaluable patients we estimate that a total of 80 children may require initial enrolment.

2. Potential risk

There is no potential risk involved in this study. Although not anticipated, development of electrolyte disturbance is a possibility which can be clinically suspected and proved through estimation of serum electrolytes, and corrective measures can be initiated quickly. Thus, this will not cause any major problem. The total amount of blood that will be required to be drawn from veins of the study subjects is only 6.0 ml. which, other than a little pain at the time of venipuncture, will not cause any harm.

3. Methods of minimizing potential risk

A detail medical history will be obtained and a thorough physical examination will be performed before enrolment of the subjects in the study which are expected to detect serious illness, and such cases will not be enrolled into the study. Study nurses will monitor the children around the clock, and one of the investigators will perform physical examination of the patients at least once daily.

4. Methods for safeguarding confidentiality

Patients will be assigned a study number, and all data entry will use this number instead of the name of the individuals. Additionally, the medical files of the patients will be securely retained under the supervision of the principal investigator, and no one other than the investigators will have access to patient information.

5. Informed consent

Since this study involved participation of minor children under guardianship, a written consent will be required from either parents/ legal guardian of the children for their participation. For those who can not read, the consent form will be read out by one of the investigators for obtaining consent.

6. Interview

The parents, or the legal guardians will be interviewed in order to know the medical history of the patients and the treatment that they have received before enrolment into the study. Similarly, the parents/attendants will be interviewed every day of the study and thorough physical examinations will be performed.

7. Benefits to the individual and society

The study children will benefit as they will be provided standard care for their illness and will remain under continued surveillance. The society may benefit if the study results indicate superiority of the reduced osmolar solution over the conventional ORS.

8. Samples required

This study will use blood, stool, urine and vomitus of the study children.

Reference

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STUDY OF EFFICACY OF A ORAL REHYDRATION SOLUTIONS IN THE TREATMENT OF ACUTE DIARRHOEA IN CHILDREN

CONSENT FORM

Your child is suffering from diarrhoea and dehydration that needs to be corrected. Currently available ORS is very effective in the management of dehydration caused by all types of diarrhoea, however, neither it can reduce stool volume nor it can shorten the duration of diarrhoea. Research are being continued to improve the currently available ORS, and we are conducting this study to determine the role of a new formulation of ORS with lower amount of glucose or rice powder, and sodium. If you agree for participation of your child in this study he will receive any of the following three ORS: standard WHO ORS, a reduced osmolar glucose-based ORS, or a reduced osmolar rice-based ORS.

For the purpose of this study your child will be required to be hospitalized until his diarrhoea stops. We'll obtain history of illness of your child, perform detail physical examination on admission and at least once a day, perform examination of his stool for determination of the cause of his diarrhoea. We'll also perform tests on his blood that will be drawn from his vein on 4 occasions during a period of 48 hours requiring a total of only 6.0 ml. (1.5 teaspoonful) of blood. Other than slight pain there is no problem associated with the procedure and drawing of this small volume of blood from your child will not cause any harm to him.

Even If you do not agree to participate, your child will continue to receive standard care of this hospital, and you will retain the right to withdraw your child any time during the study without affecting his further treatment at this hospital.

All information obtained from your child will be kept confidential, and none other than the investigators of this study will have access to those information. If you are interested to know any specific or all information regarding your child, we'd be happy to provide those subject to availability of such information.

Please put your signature/ left thumb impression at the specified space below if you are voluntarily agreeing participation of your child in the study.

Signature of the Investigator	Signature/LTI of the parent/ guardian	Signature of witness
Date:_____	Date: _____	Date: _____

Table 1: Composition and preparation of different ORS

Composition	Ros-RORS	Ros-GORS	WHO ORS
Sodium (mmol)	75	75	90
Potassium (mmol/l)	20	20	20
Chloride (mmol/l)	65	65	80
Citrate (mmol/l)	10	10	10
Glucose (mmol/l)	-	75	111
Rice powder (g)	35	-	-
Osmolality(mOsmol/l)	170	245	311

Ros-RORS = reduced osmolar rice-based ORS; Ros- GORS = reduced osmolar glucose based ORS; WHO ORS = WHO/UNICEF ORS.

note: rice powder will not influence the osmolarity of the solution because of slow breakdown of complex polysacharides.

Review # 1

Title: Estimation of absorption of electrolytes and macronutrients between reduced osmolarity ors (rice-based hypoosmolar ORS and..... in acute watery diarrhoea.

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	NOT	STATED.	
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 ✓

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 thay are justified.

(Use additional pages if necessary)

Title:

PI:

Reviewer:

COMMENTS:

1) General

a) This study attempts to answer an important question. However the protocol is poorly written there are numerous typographical errors in the text.

b) Throughout the protocol, the term Hypo-osmolar is used. It would be more accurate to refer to the solution as a reduced osmolarity solutions.

2. Abstract:

a) The composition of the intravenous solution should be stated.

b) What does the term "Darkfield positive cases" mean? If it is an attempt to identify patients with cholera, it should be stated.

3. Section entitled "Background."

a) Page 4 - It is not accurate to say that the WHO ORS stimulated "Optimum sodium absorption except in 2 to 4% of ..." There is no evidence that the absorption is "Optimum" with 2% glucose. There is adequate absorption in the majority of individuals. However, 2-4% may develop temporary malabsorption.

b) Page 6, lines 2-5 - These two sentences don't make any sense.

4. Methods:

a) What is the role of "a charcoal marker?"

b) There is no need to correct the total deficit of severely dehydrated infants with I.V. fluids. I would suggest that the IV fluids should only be used for initial resuscitation until the individuals pulse and blood pressure returns to normal and he is able to drink ORS.

c) The whole methods section needs to be rewritten with better organization. For example, the inclusion criteria is given in the first sentence but the exclusion criteria is not given until the end of the protocol.

d) Page 8, third line from bottom - it is not adequate to examine patients twice a day especially during the first day of therapy.

e) Urine electrolytes should be measured otherwise it will not be possible to accurately calculate the net absorption of sodium and water.

f) Randomization methods should be given at the beginning of the protocol.

5. Outcome Variable

a) It is not clear how the variable given in this section will be calculated. This needs to be stated clearly in the section entitled,"Data Analysis."

Response to the comments of Reviewer # one:

1. General:
   (a). Typographical errors have been corrected.
   (b). Instead of hypoosmolar reduced osmolar solution has been used.

2. Abstract:
   (a) Composition of intravenous solution stated.
   (b) "Darkfield positive cases"- indicates presence of *Vibrio cholerae* (shooting stars under microscope while examining stool under field microscopy; However, sentence has been changed to *Vibrio cholerae* positive cases.

3. Background: modified as per suggestion.

4. Methods:
   (a) "Charcoal marker" (marker is used to measure transit time i.e., for exact estimation for 48 hours of balance study period.
   (b) For severely dehydrated children only partial correction of their dehydration will be made to restore circulation and will be evaluated by pulse volume and blood pressure.
   (c) Methods section has been rewritten.
   (d) Vital signs will be monitored every 4 hours (page #8).
   (e) Urine electrolytes will be measured.
   (f) Randomization method has been given (page # 6).

5. Outcome variable
   (a) Net absorption of electrolytes will be estimated by co-efficient of absorption of primary response variables (page # 4 & 5).

Review #2

ESTIMATION OF ABSORPTION OF ELECTROLYTES ..... STANDARD GLUCOSE-BASED ORS IN ACUTE WATERY DIARRHOEA:

The objective of this study is to measure the coefficients of absorption of sodium, potassium, chloride, bicarbonate and glucose from 3 oral rehydration salts (ORS) solutions with different osmolarities given to infants and children with dehydration due to acute diarrhoea.

In view of the discussion and conclusions of the recently held *Joint WHO/ICDDRB Consultative Meeting on ORS Formulation*, the information provided by such a study could be very useful. However, I believe that useful information could also be obtained by carefully measuring intake and output of glucose and electrolytes in a subgroup of patients being randomized into a clinical trial to evaluate the efficacy of these solutions, without having to develop and conduct a specific study to measure co-efficient of absorption of glucose and electrolytes.

In addition, the design of this study, as well as the methodologies described in the proposal are unclear, incomplete and overall were very confused. For these reasons, I cannot support this application in its present form.

If the authors decide to rewrite their proposal, I would suggest they follow a clear plan that should include:

- exclusion and inclusion criteria
- sample size estimate
- enrolment of subjects
- standard case management including feeding
- withdrawals from the study
- organisation of the trial including a clear description of the methodologies to be used.

In the present proposal, information on all of these points are disseminated throughout the proposal without any logical order.

1. **Inclusion and exclusion criteria** should be regrouped and described with more detail.

   - Why select only patients with an history of diarrhoea for less than 24 hours?
   - What is the definition of diarrhoea used in this study (number of stool/24 hours prior to admission)?
   - Signs of some or severe dehydration should be clearly defined.
   - Excluding patients who had received antibiotics in the 7 days prior to admission seems to be a very strict criteria. Is there a justification for that criteria?
   - What is H/O diarrhoea?
   - Complications that will justify the discontinuation of the study should be spelt out and clearly defined.

2. **Enrolment of subjects and randomization:** This section is not clear and appears to be described in bits and pieces throughout the proposal.

   The randomization and the stratification schema should be described more clearly as well as the methodology to assess rotavirus infection on admission (with reference).

   Any indication of a baseline examination is also absent.

3. **Standard case management:** This part is crucial to the interpretation of the data and therefore should be clearly standardized and described in every detail. In the present proposal, this part is very superficially described and does not appear to be well standardized.

   - Amounts of IV fluids administered to the severely dehydrated patients.
   - Amounts of ORS solution given in ml/kg.
   - Methods of administrating ORS solution - if mothers are asked to give the required ORS then a precise way of monitoring the amounts required and given should be described.
   - Feeding is an important part of the standard case management of these patients. However, it is not clear how feeding "as used in home" will be determined, prepared in the hospital and given to the child.

4. **Withdrawals from the study:** No indication is given on withdrawal from the study and ways the patients withdrawn will be managed.

5. **Organization of the trial and methodologies:** This is the most deficient part of the protocol. In a balanced study, I believe it is extremely important to standardize the ways the output and intake are collected especially the timing of the collection.

   It is mentioned early in the proposal that charcoal will be given on admission. I suppose this is a marker for the collection of the output; however, it is never mentioned in the proposal.

Finally, I have a last comment concerning the composition of the ORS solution the investigators are proposing to test. Following the discussions at the *Joint WHO/ICDDRB Consultative Meeting on ORS Formulation*, I feel the glucose-based low osmolarity ORS solution should contain 75 mmol/l sodium and 75 mmol/l glucose. If a group receiving rice-based ORS solution is kept (which does not appear all that necessary after the conclusion of the above-mentioned meeting), its composition should be similar to the rice-based ORS solution that have been tested in clinical trials (50 g/l of precooked rice, 90 mmol/l of glucose.

Response to the comments of Reviewer # two:

1.Inclusion and exclusion criteria: page # 5

- patients with an history of diarrhoea for < 72 hours will be enrolled.
- definition of diarrhoea: three or more watery or liquid stools in last 24 hours.
- dehydration status: as per WHO criteria.
- patients received antibiotic within 3 days prior to admission will not be enrolled.
- H/O diarrhoea: watery or liquid stools for more than three times in last 24 hours.
- complications: such as septicemia or pneumonia that requires special management will be considered as deviation from the protocol regime.

2. Enrollment of subjects and randomization: page # 5 (last paragraph).

3. Standard case management: page # 6 (paragraph 4 & 5) and # 7

- for severely dehydrated subjects only partial correction of dehydration will be made to restore circulatory volume and will be measured by pulse volume, and blood pressure.

- amount of ORS: measured amounts of assigned ORS in bottles of 500 ml will be provided to every study patient. Stool output and vomitus will be replaced on weight for weight basis.(page # 7, paragraph # 1).
- feeding: defined hospital will be provided to each subject appropriate for age.

4. Withdrawal from the study: pl. see page # 7 (paragraph # 7).

5.Organization of the trial and methodologies: pl. see page # 7 (paragraph # 8 & 9) and page # 9.

Last point: composition of the ORS is according to the *Joint WHO/ICDDR, B Consultative meeting on ORS Formulation* held in December, 1994.

a) BUDGET PROPOSAL

Line item	TOTAL	
	Ist year	US$
:RSONNEL LOCAL: SALARIES		
Dr R.N. Mazumder, PI, 30% time	3,860	3,860
Dr M.K. Bhattacharya, Co-Invest., 10% time	0	
Dr. Ali Miraj Khan, Co-Invest., 5% time	650	650
Res. Physician (CSA), 100% - 2	4,500	4,500
Ms Makhduma Khatun, Sr Res Officer, 30%	2,352	2,352
Nurse (CSA) - 4	6,000	6,000
Attendant - 2	750	750
Sub-total:	18,112	18,112
)NSULTANT		
. Dilip Mahalanabis	2,000	2,000
Sub-total	2,000	2,000
)TERNATIONAL TRAVEL		
or attending conference/seminar etc.	2,000	
b-total:	2,000	2,000
)PPLIES & MATERIALS		
)rugs/medical supplies	500	500
)ffice Supplies	1,000	1,000
aboratory Supplies	1,000	1,000
)thers	500	500
Sub-Total	3,000	3,000
)TER DEPARETMENTAL SERVICES		
omputer Charges	500	500
ransport; Land & Water	500	500
edical Illustration	200	200
erox, Library Service	500	500
ab. and Pathological test	18,000	18,000
atient hospitalization (164x5x25)	10,500	10,500
taff Clinic Charges	300	300
tc		
Sub-Total	30,500	30,500
\PITAL EXPENDITURE: Equiptment, Printer etc.	4,000	4,000
Sub-Total	4,000	4,000
)TAL OPERATING COST	57,612	57,612
erhead (31%)	17,860	17,860
)TAL PROJECT COST	75,472	75,472