Attachment 1. Date 02/07/1995

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

Principal Investigator Dr. R.N.Mazumder Trainee Investigator (if any) NO

Application No. 95-~~024~~ 019 Supporting Agency (if Non-ICDDR,B) UNICEF

Title of Study Multicentre study to evaluate the efficacy of reduced osmolar ORS solution in children with acute watery 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 ~~or~~gans 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 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.

e 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

RESEARCH PROTOCOL

1.	Project Title:	PROPOSAL FOR A MULTI CENTRE STUDY TO EVALUATE THE EFFICACY OF REDUCED OSMOLARITY ORS SOLUTION IN CHILDREN WITH ACUTE WATERY DIARRHOEA
2.	Principle Investigator:	Dr. Ramendra N. Mazumder
3.	Co-investigator:	Dr. N.H.Alam
4.	Consultants:	Dr. GJ Fuchs Dr. M Santosam (WHO Representative)
5.	Proposed starting date:	July 1995
6.	Proposed duration:	Twenty four months
7.	Budget Total:	$ 82,975
8.	Donor Agency:	UNICEF
9.	Approval:	This protocol has been approved by the Clinical Sciences Division (CSD)

Signature
Division Director, CSD

Date: 3/7/95

10. Abstract Summary

Preliminary observations from the Clinical studies have shown that Reduced osmolarity ORS is superior to Standard WHO/UNICEF ORS in terms of low purging rate, less stool frequency and reduction in duration of hospitalization. This multicenter study proposal aims to evaluate the efficacy of a Reduced osmolar ORS in 600 children with acute watery diarrhoea, of them 120 patients will be studied at Clinical research & Service Centre of ICDDR,B. 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 rehydrated with intravenous Dhaka solution (Sodium -133 mmol/L, Chloride - 98 mmol/L, Potassium - 13 mmol/L and Bicarbonate - 48 mmol/L).

Present proposal will be a double blind, randomized controlled study. Control group will receive Standard WHO/UNICEF ORS and study group will receive Reduced osmolar ORS (composition in mmol/L; Sodium-75, Potassium-20, Chloride - 65, Trisodium Citrate dihydrate - 10, and glucose 75; total Osmolarity - 245 mOsmol/L). The study will be continued for following 96 hours. All intakes and output including ORS, plain water, stool, urine and vomitus will be measured. *Vibrio cholerae* positive cases will be treated with oral erythromycin. Food will be offered after initial correction of dehydration. Subjects will be admitted in the metabolic ward of the Hospital and will be under constant medical supervision. The patients will be discharged after the end of the study and when justified by clinical evaluation.

All medical records will be kept confidential and will remain with the investigator. After completion of the study, stool output/kg, stool frequency, duration of diarrhoea, etc. will be compared between Study and Control groups.

11. Reviews

(a) Research Review Committee _____
(date)

(b) Ethical Review Committee _____
(date)

1. Purpose of the trial

1.1 Background

For 20 years, WHO and UNICEF have recommended that infants and children with dehydration due to acute diarrhoea of any aetiology as well as adults will be treated with an oral glucose/electrolyte solution containing 90 mmol/l sodium and 111 mmol/l glucose (total osmolarity 311 mmol/l) provided they are able to drink and do not have severe dehydration [1, 2]. Because of its proven efficacy, safety and low cost, WHO/UNICEF oral rehydration salts (ORS) solution has been very widely used; combined with continued feeding, it has simplified treatment schemes and contributed greatly to declining case-fatality rates for acute diarrhoea in developing countries [3].

There is, however, some disagreement about the ideal composition of ORS solution, especially as regards sodium concentration and total osmolarity. The European Society of Paediatric Gastroenterology and Nutrition recommends an ORS solution containing 60 mmol/l sodium for children in developed countries [4]. This recommendation reflects concern about the risk of hypernatremia when solutions with higher sodium concentrations are given to well-nourished children [5]. The European Society also recommends that the osmolarity of ORS solution be between 200 and 250 mmol/l, based on experiments in animals showing that water absorption from such solutions is better than that from solutions isotonic with plasma [6, 7, 8, 9].

These recommendations are supported by the results of seven clinical trials conducted recently in children with acute watery diarrhoea (five studies) and in adults with cholera (two studies) to assess the clinical efficacy and safety of reduced osmolarity ORS solutions. The solutions used in these studies had an osmolarity of 225-250 mOsm/l, achieved by reducing the concentrations of glucose and sodium to 75-90 and 60-75 mmol/l, respectively. Results from these completed clinical trials were reviewed in a Joint WHO/ICDDR,B Consultative Meeting on ORS Formulation, that was held in Dhaka in December 1994 [10]:

- In 5 studies of 734 children with acute watery diarrhoea,[11, 12, 13, 14, 15] use of a reduced osmolarity ORS solution caused clinically significant reductions in 24 hour stool output and in the need for supplemental intravenous therapy when compared to treatment with standard ORS solution. Output of diarrhoeal stool was reduced by a mean of 25% during the first 24 hours and use of supplemental intravenous therapy was reduced by 33%. A multi centre study showed that the relative risk of requiring supplemental IV infusion was doubled in non-breastfed children receiving standard WHO ORS solution, while, in breastfed children, this relative risk was not affected by the type of ORS solution given.

- The 2 studies in adults with cholera[16, 17] did not permit a definite conclusion about the efficacy of reduced osmolarity ORS. A small study, in patients with voluminous diarrhoea, showed that 24 hour stool output was reduced by 28% in comparison to patients given standard ORS. Serum sodium concentration fell below 125 mmol/l in 3 of 34 patients given reduced osmolarity ORS solution (95% CI = 0 to 6), none of whom became symptomatic. In the second trial, no significant difference in stool output was observed in the treatment groups, nor was hyponatremia seen. When data from these studies were pooled, there was a 15% reduction in 24 hour stool output and a 33% reduction in the need for supplemental intravenous therapy among patients given reduced osmolarity ORS.

In addition, in the two studies (one in adults with cholera and one in children with acute watery diarrhoea) that measured vomitus, administration of reduced osmolarity ORS solution

was associated with a significant decrease in either frequency or volume of vomitus when compared to treatment with standard WHO ORS solution.

Based on the review of experience with reduced osmolarity ORS, it was concluded that:

(i) a reduced osmolarity solution with a composition similar to those tested would be have clinically significant benefits in comparison to treatment with standard ORS for children with acute watery diarrhoea, and

(ii) there is insufficient data to reach firm conclusions with regard to the possibile risks and benefits of reduced osmolarity ORS for treatment of patients with cholera.

Given the promising results from studies of reduced osmolarity ORS, and especially their convincing benefits for children with acute watery diarrhoea, a consencus was reached during that meeting on the composition of the preferred ORS formulation for use in children with acute watery diarrhoea as well as adults with cholera:

Glucose	75 mmol/l
Na+	75 "
K+	20 "
Cl-	65 "
Citrate	10 "
Osmolarity	245 mOsm/l

This formulation was selected because:

(i) its osmolarity is less than 250 mOsm/l;
(ii) its sodium content is only modestly less than in standard ORS, which may be important for treatment of cholera; and
(iii) its glucose content at least equals that of sodium;
(iv) the formulation has already been evaluated in two trials: one of 190 children with acute watery diarrhoea and another in 131 adults with cholera, both of which demonstrated that reduced osmolarity ORS solution is more efficacious than standard WHO ORS solution based on need for unscheduled IV therapy and/or reduced stool output;

To fully evaluate the clinical efficacy/safety of the above formulation the participants recommended that it is to be compared to that of the standard ORS in 2 additional multi centre studies conducted on (i) adults with cholera, and on (ii) children with acute watery diarrhoea.

This proposal describes the study to evaluate reduced osmolarity ORS solution in children with acute watery diarrhoea. It will involve 5 centres:

Bangladesh: International Centre for Diarrhoeal Diseases Research, Bangladesh (ICDDR,B), Dhaka,

Brazil: Universidade Federale do Bahia, Salvador,

India: All India Institute of Medical Sciences (AIIMS), New Delhi,

Peru: Universidad Peruana Cayetano Heredia, Lima,

Viet Nam: Children's Hospital No 1, Ho Chi Minh City,

1.2 Specific objectives

1.2.1 · Primary objectives

In children with acute watery diarrhoea, treatment with reduced osmolarity ORS solution will

- reduce 24 hours stool output and total stool output by 25%,
- reduce the duration of diarrhoea by 20%, and
- reduce the proportion of patients vomiting during the first 24 h by 30%,

1.2.2 secondary objectives

(i) In children with acute diarrhoea, treatment with reduced osmolarity ORS solution will

- reduce the need for unscheduled IV infusion by 50%,

(ii) Reduced osmolarity ORS solution will not markedly increase the incidence of hyponatremia in children with acute watery diarrhoea when compared to those treated with standard WHO/UNICEF ORS solution.

1.3 Outcome variables (see section 2.5.4 and annex 1 for definitions)

- 24 hours stool output, in g/kg of admission body weight, from the time of randomization;
- total stool output, in g/kg of admission body weight, from the time of randomization until cessation of diarrhoea;
- proportion of children in each study group requiring unscheduled IV infusion, as % of total number of children randomized in each group;
- duration of diarrhoea, in hours, from the time of randomization until cessation of diarrhoea;
- proportion of children in each study group vomiting during the first 24 hours after randomization, as % of total number of children randomized in each group;
- proportion of children in each study group with hyponatremia 24 hours after randomization in the study, as % of total of number of children randomized in each group.

2. Study design

2.1 Eligibility and ineligibility criteria

Children with the following characteristics will be eligible for inclusion in the study:

- male children,
- aged 1 - 24 months,
- with acute watery diarrhoea, defined as more than 3 watery stools in the 24 hours prior to admission,
- for less than 72 hours, and
- with signs of dehydration (some to severe dehydration) (see annex 3 for definition of dehydration status). Children with severe dehydration on admission will be given rapid IV rehydration before being randomized in one of the two treatment groups (see section 2.5.1).

Children with the following characteristics will be excluded from the study:

- children with severe malnutrition (admission weight-for-height $\leq$ 65% of NCHS standard, or with obvious oedema),
- bloody diarrhoea, as reported by the mother or caretaker of the child,
- clinical signs of systemic infection requiring antibiotic therapy.

2.2 Sample size estimate

(i) Total stool output and 24 hours stool output

Standard deviation of mean total stool output in children with acute watery diarrhoea treated with WHO/UNICEF ORS solution is about equal to the mean (10,16). Therefore, the equation for sample size calculation, assuming a 80% power to detect a 25% reduction in mean stool output:

$$n = 8*2*(SD)^2/(mean/4)^2$$

can be simplified

$$n = 8*2*(mean)^2/(mean/4)^2$$

$$n = 256 \text{ per treatment group}$$

(ii) Duration of diarrhoea

The mean duration of diarrhoea in 1 -24 months old children with acute watery diarrhoea is about 40 hours (SD 25) (16). To detect a 25% reduction in duration of diarrhoea in children treated with reduced osmolarity ORS solution, with a power of 80%, the number of children to include per treatment group will be:

$$n = 8*2*(25)^2/(40/4)^2$$

$$n = 256 \text{ per treatment group}$$

(iii) Vomiting in first 24 hours

The proportion of 1-24 months old children who vomitted during the first 24 hours after initiation of treatment with standard WHO/UNUCEF ORS solution is 30% (10,16). To detect

a 30% reduction of this proportion in children treated with reduced osmolarity ORS solution with a 80% power, the number of required per treatment group is:

$$n = 8*[(30*70)+(20*80)]/10^2$$

$$n = 296 \text{ children per treatment group}$$

In conclusion, a minimum of 300 children per treatment group will be required to detect a 25% reduction in stool output, a 30% reduction in incidence of vomiting, and 20% reduction in duration of diarrhoea with the reduced osmolarity ORs solution. This means that at least 120 chuildren will be recruited in each of the 5 centers involved in this multicenter clinical trial (total = 600 children with acute watery diarrhoea).

However, this sample size will not allow the precise determination of the impact of reduced osmolarity ORS solution on unscheduled IV infusion. The proportion of 1 - 24 months old children requiring unscheduled IV infusion when treated with WHO/UNICEF ORS solution is 10% (10,16). To detect a 50% reduction in the need for IV infusion in children treated with reduced osmolarity ORS solution with a 80% power, the number of children to include per treatment group will be:

$$n = [8*(10*90)+(5*95)]/5^2$$

$$n = 440 \text{ per treatment group}$$

The measurement of the impact of treatment with reduced osmolarity ORS solution on the need for unscheduled IV therapy is beeing considered in Data Analysis section (see section 3).

2.3 Enrolment of patients

2.3.1 Ethical review

The written approvals of the ethical review panels of the different institutions involved in this multi centre study have been requested and will be forwarded as soon as they are received.

2.3.2 Informed consent

The parents or legal guardians of the children eligible to enter the study will be fully informed about the trial, and the Principal Investigators will obtain their freely given consent to participate in the study.

The content of the information provided to the parents or legal guardians of the children is described in the attached consent form (see annex).

2.3.3 Baseline examination

A baseline history and examination will be obtained in order to:

- determine the subject's eligibility for inclusion in the study;
- collect the relevant data prior to beginning the study that will allow, (i) comparison of the study groups between centres, (ii) comparison of the study groups after randomization, and (iii) description of the study population to determine whether the results obtained can be compared with those from other trials.

The baseline history and examination will include:

- identification of the patients,
- a description of the symptoms prior to admission and their duration,
- details of any treatment given for the illness before admission,
- a description of the feeding status prior to admission (and also before the onset of illness, as these may differ),
- results of the physical examination, including the state of hydration determined according to standard criteria (see annex 3),
- results of microbiological, microscopic and biochemical examinations performed on randomization.

The forms on which the results of the baseline history and examination will be recorded will be identical in all the centres involved in this multi centre study (summary data forms are in annex 4).

2.4 Allocation to treatment group (randomization)

2.4.1 Randomization technique

As this study will be a double-blind clinical trial, the standard WHO/UNICEF ORS and the reduced osmolarity ORS will be identical in appearance and packaged in identical polyethylene sachets. The ORS packets will be arranged in a sequence of standard WHO/UNICEF ORS and reduced osmolarity ORS corresponding to the randomization code and then numbered sequentially. A careful record of the treatment number assigned to each subject will be kept.

Based on the expected proportion of children being predominantly breastfed per age group (see annex 5) and per centre, randomization will be stratified according to age (stratum A: age 1 - 6 months, stratum B: age 7 - 24 months). Separate randomization lists will be prepared for each centre and each strata. ORS packets will then be numbered appropriately (stratum A: packet numbers 001 to 500, stratum B: packet number 501 to 999).

2.4.2 Preparation and safekeeping of the randomization list

The randomization lists and numbered ORS packets will be prepared at WHO, Geneva. To establish the randomization list, permuted block of variable length will be used. In order to avoid large imbalance between treatment groups, permuted blocks of length 6 - 8 - 10 will be used for the first 60 patients in each treatment group and each centre and permuted blocks of length 2 - 4 - 6 for the remaining patients per startum and per centre.

2.4.3 Time of randomization

Randomization will take place immediately after the patient has been found eligible to enter the study:

(i) for patients admitted with signs of severe dehydration, just after rapid IV infusion has been completed, and

(ii) for patients with some dehydration, upon completion of the examination.

2.4.4. Preparation of ORS solution

As the slight difference in weight of the two types ORS packets may impede the double blind

design of this study, the ORS solution will be prepared by someone not otherwise involved with the study (especially with recruitment of the patients or management of the cases). the content of one packet will be dissolved in one liter of clean water and kept in a vessel labelled with the patient's name and study number. any unused ORS solution will be discarded aftre 24 hours. To detect glucose malabsorberer, 40 patients (20 in each group) will receive D_2-glucose (2.0 g/l).

2.4.5 Safety monitoring

Serious clinical adverse events i.e., death and seizures), will be immediately reported to the study coordinator (WHO). The study coordinator will then ask the Treatment Effect Monitoring Committee (TEMC) to review the data and eventually to decide on the continuation or interruption of the trial. The TEMC will be composed of one statistician and two pediatricians, otherwise not involved with the multi centre study.

2.5 Case management

2.5.1 Initial IV therapy

children admitted with severe dehydration will be rehydrated intravenously before being included in the study. The following IV infusion solutions will be used:

	Sodium (mmol/l)	Potassium (mmol/l)	Base (mmol/l)
Dhaka solution (**Bangladesh**)	133	13	48
Polyelectrolyte solution(**Brazil, Peru**)	90	20	30
Ringer' s lactate (**India, Viet Nam**)	130	4	28

Rate of administration will be 40 ml/kg/h for 2 hours. then the child's clinical status will be reassessed. if no longer severly dehydrated (i.e., no dehydration or some dehydration0, the child will be eligible for inclusion in the study and randomly allocated to one of the treatment groups. If at the end of the initial 2 hour IV infusion, the child is still severly dehydrated, this initial IV infusion therapy will be repeated at the same rate for another 2 hours.

All data collected during that period will be recorded on the attached forms (annex 4).

2.5.2 Oral rehydration phase

Children admitted with some dehydration will be randomized immediately following the completion of the initial physical exmination and be treated as described below.

They will be offered 100 ml/kg of the assigned ORS over 6 hours with an interim evaluation of their hydration status at 3 hours. However, if a child wants more than the estimated amount of ORS solution, and there are no signs of overhydration, he will be given more. During this phase breast feeding will be continued ad libitum. Water will not be offered. Cow's milk, formula and other foods will be withheld, and plain water will not be offered during the rehydration phase.

2.5.3 Maintenance phase

Maintenance phase will be from the end of the rehydration phase until cessation of diarrhoea or day 7, which ever comes first. During this phase, children will receive:

(i) ORS Treatment will continue with the assigned ORS solution on a volume to weight replacement of ongoing losses (watery or loose stools and vomit). However, if a child wants more than the estimated amount of ORS solution, and there are no signs of overhydration, he will be given more.

(ii) Diets

a. Ages 1- 4 months

Exclusively or predominantly breastfed infants will continue breast feeding ad libitum.

Partially breastfed infants (i.e., those receiving less than 5 breast feedings per day) will continue breast feeding ad libitum, and will also be offered at least 55 cal/kg per day of cow's milk formula, according to breast milk intake.

Non breastfed infants will be offered at least 110 cal/kg of the same cow's milk formula in eight divided feeds.

b. Ages 5 - 24 months

Partially breastfed infants (i.e., those receiving less than 5 breast feedings per day) will continue breast feeding ad libitum, and will also be offered at least 75 cal/kg per day of cow's milk formula and/or a rice-based diet (see below), according to breast milk intake.

Non breastfed infants will be offered at least 110 cal/kg per day of the same cow's milk formula and/or a rice-based diet in six divided feeds.

c. Nutrient composition of rice-based diet

Country	Protein (%)	Fat (%)	Carbohydrate (%)	Kcal (per 100 g)
Bangladesh	15	30	55	70
Brazil	10	40	50	70
India	11	38	51	85
Peru	10	45	45	95
Vietnam	17	27	56	85

(ii) Water Plain water may be provided upon request at any time during the study. At time of meals, water will be offered *ad libitum*.

2.5.4 Criteria for unscheduled IV therapy

During the rehydration phase, **worsening** or **no improvement** of hydration status at 6 hours, despite appropriate ORS administration, is an indication for IV therapy.

2.7.1 Description of the site

(i) **Bangladesh** (ICDDR,B, Dhaka - P.I.: Dr. R.N. Mazumder)

The study will be conducted at the Clinical Research Centre (CRC) of the ICDDR,B. About 60,000 patients annually attend the CRC. About 5 to 10 children every day present with acute watery diarrhoea and fulfill the eligibility criteria for this study. Children fulfilling the eligibility criteria and attending the clinic between 8 am and 12 noon on week days will be considered for inclusion into the study. Not more than 4 children will be recruited each week to enable research staff to carry out all specific activities.

(ii) **Brazil** (UFBA, Department of Pediatrics, Salvador - P.I.: Dr H. Ribeiro)

The study will be conducted in the metabolic unit of the department of Pediatrics (Unidade Metabolica Fima Lifshitz). About 1000 children fulfilling the eligibility criteria attend the metabolic unit annually. Children will be recruited day and night. However, because the metabolic unit has only 6 beds, not more than 6 children will be studied at the same time.

(iii) **India** (AIIMS, Department of Pediatrics, New Delhi - P.I.: Dr M.K. Bhan)

The study will be conducted inn the Clinical Research Facility of the Division of Gastroenterology, Department of Pediatrics, AIIMS. About 2000 children with acute diarrhoea seek treatment from the clinical facility annually. Of these, nearly 750 have acute diarrhoea with clinical signs of dehydration, of which 200 fulfill the eligibility criteria for this study. Children will be admitted in the study 24 hours a day. However, because the clinical research facility has only 8 beds, not more than 8 children will be studied at the same time.

(iv) **Peru** (UPCH, Department of Pediatrics, Lima - P.I.: Dr E. Chea-Woo)

The study will be conducted in the Diarrhoeal Diseases Research Unit/Rehydration Ward (DDRU) of the Cayetano Heredia Hospital. About 500 children fulfilling the eligibility criteria for this study are being hospitalized in the DDRU every year. Children can be recruited in the study 24 hours a day. Out of the 18 beds of the DDRU, 6 are entirely devoted to research. Therefore, a maximum of 6 children can be studied at the same time in this unit.

(v) **Viet Nam** (Children's Hospital #1, Ho Chi Minh City - P.I.: Dr Pham Ngoc Thanh)

The study will be conducted at the Diarrhoea Training Unit of the Children's Hospital #1. About 13,000 children attend the DTU annually of whom 300 fulfilled the eligibility criteria for this study. Children will be recruited in the study 24 hours a day. However, as only 5 beds are reserved for research purpose, not more than 5 children will be studied at the same time.

2.7.2 Study schedule

- procuring supplies and establishing methods: May/July 1995
- recruiting and training study personnel: May/July 1995
- initiation of data collection

Bangladesh	June 1995
India	June 1995
Viet Nam	June 1995
Brazil	July/August 1995
Peru	July/August 1995

-	end of data collection	Bangladesh	June 1996
		India	June 1996
		Viet Nam	June 1996
		Brazil	August 1996
		Peru	August 1966
-	analysis of data		July/October 1996

2.7.3 Methods

- Stool weight will be measured by using pre-weighed diapers (India, Viet Nam) or via metabolic beds (Bangladesh, Brazil, Peru).
- Urine volume will be measured with collection in urine bags.
- Water intake will be recorded until cessation of diarrhoea.
- Vomitus weight will be measured with pre-weighed pads.
- Nude body weight on admission, after rehydration, daily and on discharge will be measured on scales sensitive to 10 grams.
- Body length will be measured on admission with a length board with slidable head piece to the nearest 0.1 cm.
- Standard laboratory techniques will be used for measurement of serum sodium, potassium, chloride, hematocrit and serum specific gravity, at randomization, after rehydration, at 24 hours after randomization. If abnormalities are found at 24 hours, these measurements will be repeated at 48 hours.
- The presence of rota virus will be assessed with Dakopatts ELISA kits on an admission stool sample.
- Presence of glucose in the stools will be assessed with Clinitest tablets at the end of the rehydration phase. A value of $>1\%$ reducing substances will be taken to indicate possible glucose malabsorption. Amount of D_2-glucose loss in stool will be determined in Gas Chromatograph & Mas Spectrometer.

All information collected will be recorded in the summary data forms (annex 4).

2.8 Quality assurance

2.8.1 Training of personnel and monitoring of study

The chances for significant variations being introduced by the observer increase dramatically with the number of observers involved. With a multicentre trial, this is especially problematic since by design there are a large number of observers at distant sites.

Therefore, to reduce observational variation, especially with the assessment of dehydration status, all principal investigators involved in this multicentre study performed exercises to standardize the measurement of this variable. The development of a standardized form for the assessment of dehydration (annex 3) and the repeated exercises have allowed to reach more than 90% agreement between the investigators on the assessment of this important variable.

To further reduce observer variation, it was also agreed that:

- all study sites will perform formal evaluations of inter-observer variation in hydration assessment on a monthly basis. This will consist of asking all study physicians to independently and consecutively assess the hydration status (non vs some vs severe) of at least five suitable subjects. Assessment will be written down anonymously and the percent agreement calculated. If the disagreement rate is more than 20%, more intensive training exercises will be performed, followed by repeated exercises in inter-observer variation. The data sheets from these exercises will be kept for quality assurance review.

- the scales will be calibrated daily with standard weights; the PI will check and initial the study checklist form for these calibrations and they will be kept for quality assurance review.

- intake and output data will be reviewed each morning by the PI; in addition, when feasible, the night time collections of stools and urine will be set aside for confirmation in the morning by the PI; these procedures will be recorded on the checklist.

- other examples of quality assurance are defined in the checklist, and will include:

  - daily assessment of subject by history and physical exam,
  - confirmation that the subject's identification number corresponds to the ORS packet number,
  - determining whether intake and output are generally well matched,
  - assessing adequate urine output (> 1 ml/kg/h) to help assure the completion of urine collection process.

2.8.2 Site visits

To ensure that the study design is implemented similarly in all centres and to eliminate any eventual variation between centres, two monitoring visits per centre will take place during the course of the study: the first one at the time the first patient is being admitted in the study. Therefore, the initiation of the study in the different centres will be phased: in Bangladesh, India and Viet Nam data collection will start in June 1995, while in Brazil and Peru it will start in July/August 1995. The second site visit will take place when half of the patients should have been recruited.

Below is a list of some of the activities that will be performed during the site visit:

- meeting with the site principal investigator and with members of the study staff;
- comparison of data contained on selected worksheets with those contained in summary data forms;
- review of data forms and related records to assess completeness and security against loss or misuse;
- observation of clinic personnel carrying out specific procedures;
- check of handbooks, manuals, forms and other documents on file at the site to assess whether they are up-to-date;
- physical or verbal walk-through of certain procedures (e.g. the series of examinations needed to determine patient eligibility, or the steps followed in the informed consent process);
- conversations with key support personnel to assess their practices with regard to data collection;
- inspection of storage facilities (for ORS packets) and of study facilities.

3. Data analysis

The characteristics of the patients on admission will be compared between centres, and between the combined treatment groups with regard to the mean and standard deviation of age (in years), weight on admission (in kg), duration of diarrhoea prior to admission (in hours), serum sodium concentration (in mmol/l), packed cell volume (in %), serum specific gravity, pulse and heart rates, and with regard to percentage of patients with severe dehydration,and vomiting.

Transformed data (using natural logarithm) on stool output, ORS intake will be used when appropriate because of the usually skewed distribution of these variables. Results will be expressed as geometric means and 95% CI, ratio of the geometric means will be used to compare treatment groups. For variables with normal distribution, results will be expressed as mean and standard error of the mean, and comparison between groups will be done by using the Student's t-test. For duration of diarrhoea, a life table from time of randomization to cessation of diarrhoea will be constructed and the two treatment groups will be compared by log rank test. For the comparison of variables (e.g. percentage of patients requiring unscheduled IV infusion, percentage of patients vomiting during the first 24 hours) between treatment groups, relative risk and 95% CI will be calculated. Serum sodium and serum potassium at randomization and 24 hours later will be compared between treatment groups by using a box-and-whiskers plot, including outliers.

The determination of the impact of reduced osmolarity ORS solution on the need for unscheduled IV therapy will be assessed using two different types of combined analysis:

- combined analysis of the data collected in this multicentre study with the data collected in the multicentre study conducted on adults with cholera. With the above calculated sample size (300 children per treatment group) and the sample size of the multicentre study of reduced osmolarity ORS solution in the treatment of cholera in adults (150 adults per treatment group), we can estimate that the number of patients who will require unscheduled IV therapy:

	Standard WHO ORS
Children with acute watery diarrhoea	300*0.1=30
Adults with cholera	150*0.2=30
Total	60 (13.3%)

With same size from the combined study (450 patients per treatment group), with a 80% power, we will be able to detect a 45% reduction in the need for unscheduled IV therapy with reduced osmolarity ORS solution:

$$n=8*[13.3*86.7)+(7.3*92.7)]/6.0_2$$

$$n=407$$

- combined analysis of the data collected in this study with data obtained in studies conducted in infants and children with watery diarrhoea with other reduced osmolarity ORS solutions.

Finally, as children with cholera might be included in some centres (especially Bangladesh, India and Peru) the analysis will be performed first with all the children randomized in the study, and then after exclusion of children with culture-proven cholera.

Annex 1

Assessment of dehydration

CONDITION* (1=normal, 2=irritable/less active, 3=lethargic / comatose)

EYES (1=normal, 2=sunken)

MUCOSA (1=normal, 2=dry)

THIRST* (1=normal, 2=thirsty, 3=unable to drink)

SKIN TURGOR * (1=normal, 2=reduced)

PULSE* (1=normal, 3=feeble/absent)

DEHYDRATION STATUS:

1=no dehydration

2=some dehydration (two signs coded 2 with at least one key sign*)

3=severe dehydration (some dehydration, plus one key sign* coded 3)

Annex 2

Definitions

Cessation of diarrhoea

The last watery or loose stool before the passage of two consecutive soft or formed stools, or the occurrence of 12 hours without any stools.

Duration of Diarrhea

The time in hours from randomization until cessation of diarrhea.

Stool output

The weight of stool in g/kg of admission body weight expressed per 24 hours, or for the entire duration of diarrhoea after randomization.

Hypernatremia

Serum sodium concentration > 150 mEq/l

Hyponatremia

Serum sodium concentration < 130 mEq/l

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Roujler to assign the code after Director approval

MEMORANDUM

To: Mrs. S. Moin
Controller, Budget

From: George Fuchs, MD
Acting Director, CCD

June 28, 1995.

Sub: New Budget Code

The following two protocols have been accepted for funding by ~~WHO~~ UNICEF during their recent meeting in Dhaka in March 1995:

1. Multicentre clinical trial to evaluate the efficacy/safety of reduced osmolarity ORS solution in children with acute diarrhoea - PI Dr. R. N. Majumder

2. Multicenter clinical trial to evaluate the safety/efficacy of reduced osmolarity ORS solution in adult patients with cholera - PI DR. N.H. Alam

A letter addressed to Dr. Olivier Fontaine of WHO, by Dr. Habte re review of the proposals by the Centres Review Committees, is attached together with a copy of the fax from Dr. Fontaine re funding.

We are keen to start the protocols as soon as possible and have discussed this with the Director who suggests that I contact you for budget code numbers (US$ 10,000 in each budget will be sufficient till the funds are received from WHO).

Copies of budgets for both the proposals are attached.

Please let me know if there is anything else you will require to enable you to take necessary action.

Thank you.

OK
MMoin

There is no overhead on these protocols. We will lose money.

The protocols have not passed through our review system the assignment of budget codes can only be given if authority from the Director is obtained

3/7/95

Approved
Director

* *Revised budget for UNICEF* (including cost for D_2 [6,6] Glucose])

Title: Budget for a multi center study to evaluate the efficacy of reduced osmolarity ORS solution in Children with Acute Watery Diarrhoea

1. BUDGET DETAILS (enter all amounts in whole US$)

1.1 Personnel

Category of Personnel (list All participants, even if financial support is not required)	% of full time effort devoted to project	Year 1 (US $)	Year 2 (US $)	Total US $
Professional scientific staff (functional tittle and name - if available)				
1. Dr. R.N.Mazumder Assistant Scientist	10	2000	1000	3000
2. Dr.N.H.Alam Senior Medical Officer (gr II)	05	1000	600	1600
3. Dr. George J. Fuchs	-	-	-	-
4. One Medical Officer	100	3000	1500	4500
Technical staff (functional title and name - if available)				
1. Research Assistant	100	2700	1400	4100
2. Nurse	100	2400	1200	3600
3. Nurse	100	2400	1200	3600
4. Nurse	100	2400	1200	3600
5. Nurse	100	2400	1200	3600
Other staff (functional title and name - if available)				
1. Secretary	05	500	275	775
2. Nil				
Sub total (list in budget Summary, item 2 at end of this section)		18,800	9,575	28,375

1.2 Operating expenses

Budget item	Year 1 US$	Year 2 US$	Year 3 US$	Total US$
Chemicals [6,6-D_2-glucose]	10,000	8,000		18,000
Supplies	150	50		200
Glassware				
List minor equipment "Glucocheck" bed side glucose checking machine	100			100
Gasoline or Petrol				
Equipment maintenance	100	100		200
Data analysis	100	100		200
Other operating expenditures (specify)				
Sub-total (list in budget Summary, item 2 at end of this section)	10,450	8,250		25,000

These are items costing US$ 100-1000 each. For items ordered from aborad, include shipment and freight insurance costs, usually approximately as 20% of catalogue price if no better estimate is available. Consolidate items costing less than US$ 100 as one entry: "miscellaneous" and indicate the total amount.

1.3 Patient cost

Budget item	Year 1 US $	Year 2 US $	Year 3 US $	Total US $
Transportation	300	200		500
Other (specify)				
Drugs	200	100		300
Publication & Printing	300	100		400
Patient food	400	100		500
Patient hospitalization	12,000	3,000		15,000
Sub-total	12,900	3,300		16,200

1.4 Animals Not applicable

Type of animals		Year 1 US $	Year 2 US $	Year 3 US $	Total US $
	Purchase				
	Maintenance				
	Purchase				
	Maintenance				
	Purchase				
	Maintenance				
Sub-total					

1.5 Travel (specify) Nil

Destination and purpose	Year 1 US $	Year 2 US $	Year 3 US $	Total US $
Sub-total				

1.6 Other expenditures (specify)

Budget item	Year 1 US $	Year 2 US $	Year 3 US $	Total US $
Laboratory cost Stool Microscopy, fecal culture, ELISA test for ROTA virus, Serum electrolytes, Blood count, Plasma specific gravity	3000	1700		4700
ORS & Stool sample assay in Gas Chromatograph and Mass Spectrometry	10,000	5,000		15,000
Sub-total	13,000	6,700		19,700

1.7 Major equipment (specify) [2]

Budget item	Year 1 US $	Year 2 US $	Year 3 US $	Total US $
Sub-total				

2. BUDGET SUMMARY

Budget item	Year 1 US $	Year 2 US $	Year 3 US $	Total US $
Personnel (1.1)	18,800	9,575		28,375
Operating expenditure (1.2)	10,450	8,250		25,000
Patient cost (1.3)	12,900	3,300		16,200
Animal (1.4)	Nil			
Travel (1.5)	Nil			
Other expenditure (1.6)	13,000	6,700		19,700
Sub-total of items above (recurring costs)	55,150	27,825		82,975
Major equipment (1.7)	Nil	Nil		Nil
GRAND TOTAL (should agree with figures in part 1, Section 1.4)	55,150	27,825		82,975

PROPOSAL FOR A MULTI CENTRE STUDY TO EVALUATE THE EFFICACY OF REDUCED OSMOLARITY ORS SOLUTION IN CHILDREN WITH ACUTE WATERY DIARRHOEA.

RAMENDRA N. MAZUMDER
AND OTHERS

CONSENT FORM

Evaluation of the efficacy of reduced osmolarity ORS solution in children with acute watery diarrhoea

You are child is suffering from cholera. The major treatment of this disease is correction of dehydration and to prevent dehydration due to ongoing stool loss. Presently, standard ORS (WHO/UNICEF ORS) is optimally effective in the treatment of diarrhoeal diseases, but still research is continuing to improve its efficacy. International Centre for Diarrhoeal Disease Research, Bangladesh in collaboration with World Health Organization (WHO) is carrying out a study to investigate the efficacy of a reduced osmolarity ORS in the treatment of acute watery diarrhoea in children. It is expected that the new ORS is better than the standard WHO-ORS. If you agree to participate in this study you may expect the following:

1. Your child will get one of the two oral rehydration fluid therapy (WHO-ORS or Reduced osmolarity-ORS).

2. Two ml of venous blood will be taken from your child at randomisation, and after 48 hours of ORS therapy for estimation of haematocrit, specific gravity, and serum electrolytes for assessment and monitoring of dehydration status and serum electrolyte profile.

3. Rectal swab or stool sample will be taken for dark field microscopy and culture of *V. cholerae*, and for detection of rota virus.

4. Your will stay in the hospital until diarrhoea stops.

If you agree to withdraw your child from the study at any time, you are free to do so, even then you will get the standard treatment of this disease at the ICCDR,B.

If the above conditions are acceptable to you, please sign/give your thumb impression on this form.

Signature Principal Investigator	Signature Witness	Signature/left thumb impression Patient/Guardian
Date:_____		Date:_____