Attachment 1.

Library

Date 13/10/94

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator DR. N.H. ALAM

Application No. 94-016

Title of Study Evaluation of the effect of hypotonic ORS in the treatment of adult cholera

Trainee Investigator (if any) _____

Supporting Agency (if Non-ICDDR,B) _____

Project status:
( ) New Study
( ) Continuation with change
( ) No change (do not fill out rest of 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 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.

(PTO)

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

Principal Investigator

Trainee

SECTION I: RESEARCH PROTOCOL

Title: **Evaluation of the effect of hypotonic ORS in the treatment of adult cholera**

Principal Investigator: Dr. Nur Haque Alam

Co-principal Investigator: Dr. D. Mahalanabis

Co-investigators: Dr. S.A. Sarker & Dr. P.K. Bardhan

Starting date: As soon as approved by RRC & ERC & funds are made available

Ending date: 2 years from the date of starting

Funding source:

Total budget: US $83,203

Scientific Division : This protocol has been approved by the Clinical Sciences Division.

Signature of the Division Director

Date: 10.10.94

Abstract Summary

Most of the perfusion studies done in animal and human model in optimising oral rehydration solution composition, maximum water absorption and optimum sodium absorption occurred from the solution of medium ranged sodium and glucose contents (Na^+ 60 approximately and glucose 80-120 mmol/l). Preliminary observations from the clinical studies also reveal that hypotonic ORS is superior to isotonic ORS (WHO-ORS) in terms of low purging rate, less stool frequency and hospitalization. In a 3 cell randomised controlled trial, this protocol proposes to study the efficacy and safety of a hypotonic ORS in the treatment of adult patients with cholera. In total 195 patients will be randomised to receive any of the three oral solutions (a) standard WHO-ORS (b) Standard rice-ORS and (c) Hyp-ORS (Na^+ 70, K^+ 15, Citrate 7, Cl^- 65, glucose 83 mmol/l, osmolality 240 mmol/l).

After completion of the study important variables (e.g. stool/kg, duration of diarrhoea etc.) will be compared among the groups.

SECTION II: RESEARCH PROTOCOL

INTRODUCTION

Objective

To evaluate the efficacy and safety of a hypotonic ORS in the treatment of adults with cholera.

Background

The widespread use of oral rehydration therapy has produced a dramatic decline in the morbidity and mortality of acute infectious diarrhoea throughout the developed and developing world (1, 2). While the efficacy of WHO recommended glucose based ORS (WHO-ORS) is well established, this formulation does not reduce stool volume, frequency or duration of diarrhoea (3, 4). Current research on oral rehydration solution (ORS) is to (a) improve its efficacy and (b) optimization and simplification of its composition. In the 1970s the World Health Organization (WHO) adopted a formula for a glucose electrolyte solution (Na^+ 90 mmol/l, glucose 111 mmol/l, osmolality 311 mosmol/l) which was a compromise solution with emphasis to treat all diarrhoeas in all ages including cholera in older children and adults which is associated with more sodium loss in stool. Despite the unquestioned success of this solution in reducing the morbidity and mortality from acute diarrhoeal disease in the developing world there continues to be a number of controversies concerning ORS composition. In developed communities the use of the high sodium WHO-ORS has been slow because of the fear of hypernatraemia (5, 6, 7). The argument in favour is that infantile diarrhoea due to common pathogens like rotavirus and diarrhoeagenic *E. coli* in developed countries, induce faecal sodium losses of approximately 40 mmol/l, and invasive pathogens (*Campylobacter, Salmonellae, Shigella*) are associated with sodium losses 50-60 mmol/l (8). Thus it is conceivable that in noncholera diarrhoeas, which have different stool electrolyte losses, the administration of WHO-ORS, although likely to be still safe, may not be ideal.

Hypotonic ORS in perfusion studies

Most of the perfusion studies done in animal and human model in optimizing oral rehydration solution composition, the concentration of sodium and glucose, osmolality and the role of base or base precursors were looked for. The studies done in rat model have shown that in normal intestine, optimal water absorption occurs from a solution containing 60 mmol/l of sodium and 80-120 mmol/l of glucose (8). Elliot *et al.* (9) perfused isotonic saline and three oral rehydration solutions containing 90, 60, and 35 mmol/l sodium respectively in the normal human jejunum. Sodium absorption was significantly greater from the ORS with 90 ($p < 0.01$) and 60 mmol/L sodium. Water absorption was also greater from the 60 and 90 mmol/l sodium ORS than from that with

the lower concentration. In a further study, to examine the effect of sodium concentration on sodium and water absorption from hypotonic ORS, Hunt *et al.* (10) in a similar model used three solutions with increasing osmolality (210, 240, and 269 mOsmol/kg) and sodium concentrations (45, 60, and 75 mmol/l) respectively and a glucose concentration of 90 mmol/l. Water absorption was greater from the ORS with a sodium concentration of 60 mmol/l than from those with sodium concentration of 45 and 75 mmol/l ($p < 0.05$). Sodium absorption was similar from ORS with sodium concentration of 60 and 75 mmol/l but greater than the solution with lower Na concentration ($p < 0.01$). Glucose and potassium absorption were greater from the ORS with 60 mmol/l sodium than from other two ORS ($p < 0.05$). In another study Hunt *et al.* (11) compared three hypotonic solutions with different concentrations (45, 60, and 75 mmol/l) and osmolality of (210, 240, and 270 mOsm/kg respectively) but identical glucose concentrations (90 mmol/l) with WHO-ORS. Greatest water absorption was seen with ORS 60:240 ($p < 0.01$). Sodium absorption from ORS 60:240 and WHO-ORS was similar and greater than sodium absorption from ORS 45:210 ($p < 0.05$). Potassium and glucose absorption were greater from ORS 60:240 than from any other hypotonic solution but equal to absorption from WHO-ORS. Similar result was observed in a study of human model of experimental cholera (12); greater water and sodium absorption was seen with ORS of sodium 60 mmol/l and glucose 90 mmol/l with osmolality of 240 mOsm/kg as compared to ORS containing sodium 35 mmol/l, glucose 200 mmol/l, and osmolality of 310 mOsm/kg. Unfortunately there was no comparison group with standard WHO-ORS.

Obviously, optimal ORS efficacy depends on a complex interaction of solute concentrations and osmolality, but these results suggest that a hypotonic solution with approximately 60 mmol/l sodium and 90 mmol/l glucose is likely to optimise water absorption.

Clinical studies with hypotonic ORS

Clinical experience with hypotonic oral rehydration solution in the treatment of diarrhoeal disease is rare. Recently, the results of one clinical trial have been reported comparing a hypotonic ORS (Na^+ 60, glucose 84 mmol/l, osmolality 224 mOsmol/kg) with isotonic solution with similar concentration of sodium (Na^+ 60, glucose 144 mmol/l, and osmolality 304 mOsmol/kg). Children given the hypotonic ORS solution passed significantly fewer diarrhoeal stools, and their diarrhoea and hospital stay were shorter than those of children given the isotonic ORS (13). However, they did not measure the purging rate. WHO has conducted a multicentre study to evaluate a hypotonic ORS with a sodium concentration of 60 and glucose of 84 mmol/l; preliminary results show that stool output and the proportion of patients requiring additional IV infusion were reduced in the group of patients treated with low osmolarity ORS solution (14). A preliminary observation with a low sodium (Na^+ 60 and osmolality 267 mOsm/l) ORS containing alanine and glucose has been found to be more effective compared to WHO-ORS in the treatment of persistent diarrhoea (Sarker *et al.*, 1994; in press) (15). In an other study

in infants with acute watery diarrhoea a solution containing Na=67 mmol/l, glucose=89 mmol/l, osmolality=249 mmol/l reduced stool frequency, vomiting, and purging rate compared to WHO-ORS (unpublished data). The efficacy and safety of hypotonic ORS in the treatment of older children and adults with cholera are yet to be studied. Important policy decisions to formulate a hypotonic ORS that would be accepted universally cannot be made until appropriate trials of such solutions are conducted on cholera patients.

In this protocol we propose to study the **efficacy and safety of hypotonic and hypo-osmolar oral rehydration solution** in the treatment of adult cholera patients.

Rationale

Existing data from perfusion and standard clinical trial in non-cholera diarrhoea using hypotonic ORS have shown better efficacy in terms of maximum water absorption and optimum sodium absorption. If hypotonic ORS is found to be similarly effective and safe in the treatment of adult cholera, the composition of WHO-ORS might have to be revised to make it universally accepted in the treatment of diarrhoeas of diverse etiology.

Methods

Patient selection:

Adult male patients attending the ICDDR,B treatment facility at Dhaka with a history of diarrhoea will be evaluated following the inclusion and exclusion criteria.

Inclusion criteria:

a) Male adult 15-55 years of age.
b) History of diarrhoea 24 hours or less.
c) Moderate or severe dehydration (clinical estimation body weight loss above 7.5%) who would ordinarily receive I.V. for initial hydration.
d) Initial dark field microscopy positive for *V. cholerae*
e) No history of any drug taken outside
f) Informed consent given
g) Baseline observation: stool rate >5ml/kg/hour during 8 hr observation

Exclusion criteria:

a) Signs of systemic infection (Pneumonia, sepsis etc.)
b) Bloody diarrhoea

Assessment of eligibility

Patients initially selected will be taken to the study ward for evaluation. After taking body weight, obtaining a standard clinical history and performing a complete physical examination, the patients will be rehydrated and maintained with intravenous fluid containing polyelectrolyte solution (Na^+ 133, K^+ 13, Cl^- 98, HCO^-_3 in the form acetate 48 mmol/l) over 8 hours. Ongoing stool loss will also be matched with intravenous fluid to keep the patient in positive fluid balance before the ORS study begin.

Study design and treatment schedule:

The study will be randomised as a 3-cell controlled-trial, and the glucose containing ORS will be blinded. The three treatment schedules are:

1) Standard WHO-ORS (Na^+ 90, K^+ 20, Cl^- 80, citrate 10, glucose 111, osmolality 311 mOsmol/l);

2) Standard Rice-ORS (Na^+ 90, K^+ 20, Cl^- 80, citrate 10, rice powder 50 g, osmolality 220 mOsmol/l);

3) Hypo-ORS (Na^+ 70, K^+ 15, citrate 7, Cl^- 65, glucose 83 mmol/l, osmolality 240 mOsmol/l, (NaCl=2.9 g, Kcl=1.125 g, Sodium citrate=2.0 g, glucose=15.0 g).

Randomization

A randomisation list will be prepared by using random number table (permuted blocks) taking block length of variable size. The randomisation list will contain a serial number and a code for one of the solutions. The patients who will receive glucose-based ORS (WHO-ORS or hypotonic glucose ORS) will be coded as A and B masking their identity. The ORS packets will also be labelled as A and B. Serially numbered envelopes having a code of the ORS according to the randomisation list will be kept sealed until the patient is ready for offering the ORS. The serial number of the envelope will correspond with that of the patient.

Case Management

After enrolment in the study the patient will be randomised to receive any of the three ORS. Patients will be instructed to receive ORS freely until diarrhoea stops. They will receive hospital standard diet without milk. Bread and sugar will be served for breakfast and rice, vegetables, fish/meat and lentil soup will be served for lunch and supper. Antibiotic treatment with erythromycin (standard treatment of cholera now at ICDDR,B) will commence with the ORS therapy at a dose of 500 mg 6 hourly. Intake of ORS, plain water and output of stool and urine will be recorded every 8 hours. Body weight and dehydration status will also be noted during the intake and output measurement.

Any patient unable to maintain hydration with ORS due to excessive vomiting and/or high purging rate (> 10 ml/kg.hr) with reappearance of dehydration signs and measured body weight ≤ admission body weight will be rehydrated fully again with intravenous fluid (unscheduled I.V) rapidly over 2-3 hours and again will be assigned to the scheduled ORS. Before starting unscheduled I.V. blood will be drawn for Hct, plasma sp. gr. and electrolytes. The stool volume during I.V. period will be collected and measured separately.

Stoppage of diarrhoea will be indicated by last watery stool followed by soft/formed stool and/or no stool for 16 hours. Duration of diarrhoea will be calculated from the commencement of ORS to the last watery stool.

Laboratory studies:

Blood for Hct, Sp. gr. and electrolyte will be taken at the beginning (before start of intravenous fluid), at the beginning of ORS intake and at 24 hours of ORS therapy. Stool/rectal swab will be examined for *V. cholerae* with darkfield microscopy during the observation period. After inclusion in the study, stool or R/S will be sent for culture of shigella, salmonella and vibrio cholerae and also stool microscopy will be done to look for any parasites.

Gut balance of sodium

Selection of subject: Gut balance of sodium (initial 24 hours) will be done in 10 cases from each group. The first 10 patients will be selected from each group whose purging rate exceeded >7 ml/kg.hr during the observation period.

Procedure: At the start of ORS administration, a charcoal marker will be fed and urine collection will start and meaurement of ORS intake will commence. The stool collection will start with the appearance of charcoal in the stool. Measurement of vomitus will also be done carefully during balance period. After 24 hrs 2nd marker will be given to the patient and urine collection will be completed and ORS intake recorded and stool collection will be stopped with appearance of the 2nd marker in the stool. Stool and urine sodium and potassium will be measured from the collected stool and urine samples and intake will be measured by ORS intake and diets. Initial 24 hours intake of sodium will be measured from the total intake of ORS and food. Intake and output of sodium will be compared among the groups.

Sample size: Expecting 25% stool output (g/kg.24 hr) reduction with the new treatment compared with the standard WHO-ORS (mean±SD, 366±174) (16) and assuming a significance level of 0.05 and 80% power, the sample size in each group is 58. Considering 10% drop out, the final sample size is 65 in each group.

Outcome variable

Primary response variables are:

(a) Stool output rate g/kg.24 hrs, (b) total stool output (to cessation) g/kg, (c) duration of diarrhoea (hrs), (d) ratio of every 8 hour purging rate to baseline 8 hour stool rate (initial observation period).

Secondary variables are:

(a) frequency of stool, (b) frequency of vomiting, (c) total sodium intake and output (mmol) in subgroup, (d) serum sodium change (may drop from normal), (e) proportion of patients required unscheduled I.V., and (f) ORS intake (ml/kg).

Data analysis

All data generated from this study will be entered into a Personal Computer using StatPack Gold statistical package. Statistical analysis will be done with SPSS PC+ statistical package. Continuous variables will be analysed using Anova, students *t*-test or non parametric tests according to the appropriateness and applicability.

Dichotomous variables will be compared among the groups using Chi-squared test or Fisher's exact test. Statistical significance will be accepted at the level of 0.05.

REFERENCE

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14. Nineth programme report 1992-93. WHO/CDD/94.46.

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CONSENT FORM

Evaluation of the effect of hypotonic ORS in the treatment of adult cholera

You are suffering from cholera. The major treatment of this disease is rehydration therapy. Presently, WHO-ORS is optimally effective in the treatment of diarrhoeal diseases. Present research on ORS is to improve its efficacy in terms of stool volume reduction and duration of diarrhoea. ICDDR,B is carrying out a study to evaluate the effect of a hypotonic ORS in the treatment of adult cholera. It is expected that this ORS is better than the WHO-ORS and Rice-ORS. If you agree to participate in the present study, you may expect the following:

1. You will get one of the three oral rehydration fluid (WHO-ORS, Rice-ORS or glucose-based hypotonic ORS).

2. 2 ml of venous blood (ante cubital) will be taken at the beginning of I.V. rehydration, at the beginning of ORS therapy and at 24 hours of ORS therapy for estimation of Hct, 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*, *Salmonella* and *Shigella*.

4. You have to stay in the hospital until the diarrhoea stops.

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

If the above conditions are acceptable to you, please sing or give your thumb impression below.

Signature of the Investigator

Signature/Thumb impression of the patient/guardian

Date:_____

Date:_____

Witness:_____

BUDGET PROPOSAL

PROJECT TITLE : Evaluation of the effect of H-ORS in the treatment of adult cholera

NAME OF DONOR :

STARTING DATE :

PROJECT DURATION : 2 years from starting

CLOSING DATE :

NAME OF P. I. : Dr N.H. ALAM
RRC APPROVAL DATE :
ERC APPROVAL DATE :

Amount in US Dollar

Line item	Ist year	2nd year	TOTAL
	A	B	C=A+B
PERSONNEL LOCAL: SALARIES			
Dr N.H. Alam, PI - 20% time	2,670	2,804	5,474
Dr S.A. Sarker, Co-Invest - 10% time	1,430	1,501	2,931
Dr P.K. Bardhan, Co-Invest - 10% time	1,470	1,544	3,014
Research Physician - 1 (100% time)	2,100	2,205	4,305
Health Assistant (CSA) - 2 (100% time)	1,800	1,800	3,600
Health Worker - 4 (100% time)	2,400	2,520	4,920
Secretarial service - 25% time	500	525	1,025
Sub-total:	12,370	12,898	25,268
CONSULTANTS: Dr. D. Mahalanabis	1,500	1,500	3,000
Sub-Total	1,500	1,500	3,000
INTERNATIONAL TRAVEL: (Ticket, Transporation etc)		2,500	2,500
Sub-Total	0	2,500	2,500
SUPPLIES & MATERIALS			
-Hospital Supplies	100	100	200
-Office Supplies	300	200	500
-Others	400	200	600
Sub-Total	800	500	1,300

Line item	Year		TOTAL
	Ist year	2nd year	US$
	A	B	C=A+B
OTHER CONTRACTUAL SERVICES			
-Rent, Communication & Utilities	200	200	400
-Printing & Publication of Forms, Annual report,	100	200	300
-Patient food & diet,ICDDR,B Guest diet & Lodging	500	500	1,000
-Service Charge ; Daily Wager, Short term Emp etc	500	500	1,000
Sub-Total	1,300	1,400	2,700
INTER DEPARETMENTAL SERVICES			
-Transport; Land & Water	100	100	200
-Medical Illustration	50	50	100
-Xerox, Libarary Service	300	200	500
-Lab. and Pathological test	4,000	3,000	7,000
-Patient hospitalization	10,000	10,000	20,000
Sub-Total	14,450	13,350	27,800
CAPITAL EXPENDITURE: Equiptment, Furniture etc	500	500	1,000
Sub-Total	500	500	1,000
TOTAL OPERATING COST	30,920	32,648	63,568
INDIRECT COST (31%)	9,539	10,097	19,635
TOTAL PROJECT COST	40,459	42,745	83,203

GFORMET.WK1

S. H
9/10/94

Answers to the comments of Reviwer No. 1

Q. 1 3-way randomisation and Rice-ORS as control

Ans. The results of several studies have already proved that rice-ORS is better than WHO-ORS in terms of stool reduction. Considering its better efficacy, rice-ORS is the standard oral rehydration fluid in the treatment of diarrhoeal diseases presently at ICDDR,B. The disadvantage of rice-ORS is that it could not be made available packaged for ready to use and it needed cooking. The proposed hypotonic ORS is expected to have better effect than that of rice-ORS. If this is true, then rice-ORS may be replaced by hypotonic ORS as a rehydration fluid in diarrhoea at ICDDR,B and other centres. For the above reasons, we have selected rice-ORS as a second control group.

The osmolality of rice-ORS has been already mentioned in the protocol (page 6)

Q. 2 Target difference of stool output and sample size in each group

Ans. Although there is no published data about the stool output with hypotonic ORS, we are expecting a target of 25% stool volume reduction with the proposed hypotonic ORS. The estimated sample size in each group is 65.

Q. 3 Block length of permuted block randomization

Ans. Block length of variable size will be used during the randomization procedure.

Q. 4 Randomisation procedure

Ans. Randomisation procedure for the sub-study (gut balance) has been mentioned in the protocol (page 7).

Q. 5 WHO report about hypo-osmolar ORS

Ans. WHO report about hypo-osmolar ORS has been cited in the background.

Q. 6 Reasons for exclusion of pateints who have taken drug outside

Ans. Inclusion of patients who have taken drug outside might influence the outcome of the study.

Q. 7 Taking ORS freely

Ans. Patients will take ORS freely for the replacement of stool output to maintain hydration.

Q. 8 Trial size may be low

Ans. We have calculated the sample size wih reference to earlier study. The estimated sample size is increased to 65 in each group.

Answers to the comments of Reviewer no. 2

1. Sample size calculation procedure has been mentioned in the text.
2. Suggestion of doing serum electrolytes, Hct and Specific gravity at the beginning of the study has been incorporated.
3. Suggestion about measurement of vomit during gut imbalance period has been incorporated.
4. Consent form attached.

Reviewer NW-1

Title: Evaluation of the effect of hypotonic ORS in the treatment of adult cholera

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project		✓	
Adequacy of Project Design			✓
Suitability of Methodology		✓	
Feasibility within time period	✓		
Appropriateness of budget ?	-	-	-
Potential value of field of knowledge	✓		

CONCLUSIONS

I support the application:

a) without qualification ☐

b) with qualification

- on technical grounds ☑
- on level of financial support ☐

I do not support the application ☐

TO:- DR. D. Mahalanabis

Reviewer - NW - 2

Title: Evaluation of the effect of hypotonic ORS in the treatment of adult cholera

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project	✓		
Adequacy of Project Design	✓		
Suitability of Methodology	✓		
Feasibility within time period	✓		
Appropriateness of budget	-	-	-
Potential value of field of knowledge	✓		

CONCLUSIONS

I support the application:

a) without qualification ☑

b) with qualification

- on technical grounds ☐
- on level of financial support ☐

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: Evaluation of the effect of hypotonic ORS in the treatment of adult cholera.

PI:

Reviewer:

The above trial is important to do, but the written methodology is deficient in several respects, as follows:

1) Why 3-way randomization. What is the osmolality of rice-ORS?
Why is rice-ORS included as a 'control group'

2)(a) What is the largest difference in cont. stool output in ml/kg/24 hours during 1st 24 hours after randomization, 2nd 24 hours after randomization
What is the rationale for establishing (a) as largest differential (i.e. specify scientific background / statistical reasoning)?
Given (a), how many patients should be randomized per treatment group
What are the contrasts of interest: (i) hypotonic ORS v. WHO-ORS
(i) hypotonic ORS v rice-ORS
(ii) hypotonic ORS v WHO & rice-ORS as combined control?

3) Permuted block randomization is suggested, but block lengths are not specified 3 or 6; 3 only; 6 only. Note that mid-term analysis after 75 patients is suggested but 75 is not divisible by 6. Since ORS solutions are not indistinguished (eg. rice v. WHO), then fixed block randomization, especially with short block length (3), is inadvisable.

4) An observation period is mentioned (? during IV rehydration) during which stool output will be measured x 10 patients per treatment group recruited

for a sub-study that commences when ORS does. There should be a separate randomisation stratum for "over 7 ml/Kg/hr" and the first 30 patients whose assignment is made via this stratum should constitute the special study participants. [Other schemes are open to abuse — such as starting a patient on the sub-study, suspending it, & restarting with another patient. Methodology should guard against this possibility, hence the above suggestion],

5) In Background mention that WHO statistical overview of glucose/[illegible] (I think) RCTs highlighted the link between hyposmolar solutions & stool output (cf. article Dr Mahalanabis)

6) Why exclude patients with any drug taken outside? Give reasons

7) On p10, the intention is that ORS be given/taken freely. Give reasons for this scheme rather than, for example, replacement of outputs [I am not suggesting that the proposed scheme is inappropriate but its implications for what conclusions may drawn about the various solutions needs to be thought about, so that investigator is satisfied that design meets her/his objective for inter-ORS comparison)

8) I suspect that trial size may be too low for definitive study. ICDDR,B does not lack patients. There is no excuse for not doing definitive study!

7th 1994

TO:- DR. D. Mahalanabis

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: Evaluation of the effect of hypotonic
PI: ORS in the treatment of adult cholera

Reviewer:

This is a very well written protocol and should be done at ICDDR,B. The background information and project design are adequate. This protocol will provide new knowledge in the management of adult cholera patients. I have a few minor comments to make

How the sample size was calculated should be mentioned

Serum electrolytes, specific gravity and blood test should be done at the beginning of the study period.

Extra care should be taken to measure the vomitus adequately during the gut balance period

consent form should be attached to the protocol