Attachment 1.

Date 22.11.82

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator DR. SYED MASUD AHMED Trainee Investigator (if any) _____

Application No. 82-054(P) Supporting Agency (if Non-ICDDR,B) _____

Title of Study A Comparative trial of WHO recommended ORS with ORS effervescent tablets

Project status:
(✓) New Study (PILOT)
( ) 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:
   NA 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
   NA 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.

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

22/11

Principal Investigator

Trainee

23 NOV 1982

82-054 (P)
22/11/82

SECTION 1 - RESEARCH PROTOCOL (PILOT)

1. **TITLE:** A COMPARATIVE TRIAL OF WHO RECOMMENDED ORS WITH ORS EFFERVESCENT TABLETS.

2. **PRINCIPAL INVESTIGATOR:** Dr. Syed Masud Ahmed

   CO-INVESTIGATORS: Dr. Rafiqul Islam

   Dr. Thomas Butler

3. **STARTING DATE:** December 1, 1982

4. **COMPLETION DATE:** March 1, 1983

5. **TOTAL INCREMENTAL COST:** US $ 2,812.00

6. **SCIENTIFIC PROGRAMME HEAD:** This protocol has been approved by the Pathogenesis and Therapy Working Group.

Signature of Scientific Programme Head: T. Butler

Date: 17-11-82

7. **ABSTRACT SUMMARY:**

A clinical trial is proposed to compare the efficacy, acceptability and safety of two forms of oral rehydration solutions, WHO recommended ORS in the usual powdered form and another ORS effervescent tablet form available commercially.

100 patients (50 adults and 50 children under 5 years of age) with acute watery diarrhoea of less than 48 hours duration will be studied. 25 patient from each group will receive WHO recommended ORS in the usual powdered form and the other 25 patients will receive ORS effervescent tablet which has identical composition when dissolved in water. Patients developing moderate and moderate-to-severe dehydration and having no complications e.g., high fever, convulsion, shock etc. will be taken into the study after informed consent is obtained from the patients or parents. Both rehydration and maintenance will be with Oral Rehydration Solution and anyone requiring I/V at any stage of therapy will be taken out of study. Intake and Output, electrolyte changes, tolerability and acceptability will be compared at 0, 24 and 48 hours of oral therapy in the two groups. The ORS in the tablet form has longer shelf life, placebo effect of medicine, and more convenient for storage, carriage and preparation. Thus it is expected to be of more value from public health point of view of control of diarrhoeal diseases.

8. REVIEWS:

(a) Research INvolving human subjects: _____

(b) Research Committee: _____

(c) Director: _____

(d) BMRC: _____

(e) Controller/Administer: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION.

1. Objectives:

The objective of this study is to compare the efficacy, acceptability and safety of two forms of oral hydration solution: WHO recommended ORS in the usual powdered form and ORS effervescent tablet.

2. Background:

Dehydration in cases of acute diarrhoea of any etiology and in all age groups can be treated orally with a simple glucose-electrolyte solution[1]. From the observation that glucose stimulated sodium absorption remained normal in cholera[2], today's home cure for diarrhoea oral fluid developed. Careful in hospital clinical trials showed that oral route can be safely used in treating acute diarrhoea[3]. It was later proved that not only can oral glucose-electrolyte solutions adequately maintain hydration in the face of continuing diarrhoeal losses[4], but also, if given early in the course of illness, can entirely obviate the need for intravenous fluids[5]. Recent experience with the use of oral fluid therapy in many developing country settings resulting in significant reduction in diarrhoea mortality[6,7,8,9,10] has made this health intervention into global recognition as one of the few widely applicable and technically simple approaches that could substantially reduce infant and child deaths around the world.

The present WHO recommended ORS packet contains bicarbonate which have short shelf life as the ingredients form lump in humid climate like Bangladesh. This is the most single important disadvantage of the present form of WHO recommended ORS. A comparative clinical trial using base precursors like citrate in place of bicarbonate by Islam et al., at ICDDR,B has shown that it is quite effective for correction of acidosis[11] within 24 hours. Also the excessive sweet taste of ORS quite often makes it difficult to pursue feeding especially in case of children as well as adults.

3. Rationale.

The WHO recommended ORS in the present powdered form has short shelf life and logistic problems like preparation, packaging, storage distribution etc concerned with the delivery of oral rehydration fluid in the remote rural areas of the diarrhoea endemic underdeveloped countries. It has also excessive sweet taste which may be responsible for unacceptability of ORS to quite a large section of both adults and children. If a ORS can be prepared in some convenient form like tablet with the same composition and with a better taste, it will be more convenient from public health point of view of production, storage, distribution etc. and thus may help solve many of the logistic problems of WHO CDD programme.

B. SPECIFIC AIMS:

1. To compare the efficacy, safety, and acceptability of ORS effervescent tablet with that of WHO recommended ORS in the usual powdered form.

C. METHODS AND PROCEDURES:

1. ORS effervescent tablets.[12]

ORS effervescent tablet, is a pleasantly flavoured glucose-electrolyte mixture, which when dissolved in water as described corrects electrolyte and water deficiencies due to diarrhoea.

Each effervescent tablet when dissolved in 120 ml (4fl oz) contains:

Glucose anhydrous	2182 mg
Sodium chloride	421 mg
Potassium chloride	180 mg
Citric Acid	691 mg
Sodium Bicarbonate	302 mg
Saccharin sodium	50 mg

Vanilla/Banana flavouring

Composition in terms m.mol, of the solution prepared by dissolving one tablet in 20 ml water:

Sodium	90 m.mol/L
Potassium	20 m.mol/L
Chloride	80 m.mol/L
Citrate	30 m.mol/L
Glucose	100 m.mol/L

The solution after preparation should not be boiled. It should be prepared fresh daily and any unused solution should be discarded.

2. Subjects:

50 adults (15 to 50 years) and 50 children (under 5 years) with the history of acute water diarrhoea of less than 48 hours duration having moderate dehydration will be taken into the study. Patient with complications like high fever, pneumonia, convulsion and H/O antibiotics intake within past one week will be excluded from the study. 2 patient's in each group fulfilling the above criteria will be entered into after informed consent has been obtained. Patients will be assigned to either group of therapy by randomization.

3. Clinical procedures:

Selected patient's will be admitted directly in the study ward. The followings will be done until diarrhoea stopped.

(a) Body weight will be taken on admission and subsequently every 8 hour.

(b) Thorough physical exam on admission and monitor for signs of hydration status 4 hourly.

(c) 2 c.c. venous blood will be drawn for HCT, electrolytes and specific gravity on admission, at 24 hours and 48 hours.

(d) Intake/output chart will be maintained 8 hourly.

(e) Catheter specimen of stool will be sent for D/F, for V. cholerae, and culture in all plates for Salmonella, Shigella, E. coli etc. Stool will be saved for Rotavirus detection by ELISA technique in case of childrens only.

(f) No I/V will be given. Rehydration as well as maintenance will be with oral fluid only. Anyone requiring I/V at any stage of therapy will be excluded from study.

Patients will be given oral fluid ad libitum to drink as long as diarrhoea continues. Free water and diet will be allowed without any restriction.

A summary of clinical measurements is as follows:

	Adm	4 hrs	8 hrs	16 hrs	24hrs	48hrs
Clinical evaluation	✓	✓	✓	✓	✓	✓
HCT & Sp. Gr.	✓	—	—	—	✓	✓
Serum Electrolytes	✓	—	—	—	✓	✓
Weight	✓	—	✓	✓	✓	✓
Intake & Output	—	—	✓	✓	✓	✓

(g) Failure of the therapy will be defined as the inability to rehydrate, maintain hydration or failure to correct electrolyte imbalance.

Criteria for failure:

(i) Loss in body weight

(ii) Reappearence of signs of dehydration

(iii) Severe lethargy, paralytic ilens, restlessness, or irritability etc.

Such patients will be considered treatment failure and will be treated with appropriate I/V fluid.

* (h) See Page 8 - Extra .

4. Analysis of Data:

All the information will be kept in a flow sheet for each patient. Admission weight, plasma specific gravity and electrolytes as well stool output and ORS intake in the two groups will be compared at 0 hrs, 24 hrs and 48 hrs. Tests will be done for statistical significance (students "t" test). Also the taste and acceptability of the two solutions will be compared.

D. SIGNIFICANCE:

From the result of the study it will be possible to determine whether a oral rehydration solution in tablet form is better than the usual powder form regarding efficacy, safety and acceptability in childrens as well as adults.

To assess the acceptability of the two solutions, the following two procedures will be done:

(A) Patients other than young children will be asked to grade the taste of the solution as:

1. Very bad
2. Slightly unpleasant
3. Neutral
4. Good
5. Very tasty

Mothers of younger children will be asked whether the children seemed to object to taking the fluid or whether it took easily. This will be done after 24 hr of therapy

(B) After 48 hr when patients have completed the study. They will be presented with small cups of the two different solutions. After tasting them, they will be asked to state which one tastes better.

E. FACILITIES REQUIRED:

(i) No new office space is required

(ii) Laboratory facility for routine Biochemistry, Microbiology and Clinical Pathology will be utilized.

(iii) Hospital Resources - the study ward will be used and on average 4 patients will be taken daily. Thus a total of 8 beds will be sufficient.

(iv) Animal Resources will be needed for E. coli study.

F. COLLABORATIVE ARRANGEMENTS: Nil

SECTION III - BUDGET

DETAILED BUDGET

1. Personnel services

Name	Position	% effort	Project Requirement Taka	Dollar
Dr. Syed Masud Ahmed	Principal Investigator	50%	4500	-
Dr. M. Rafiqul Islam	Co-Investigator	5%	1500	-
Dr. T. C. Butler	Co-Investigator	1%	-	-
3 Senior Staff Nurse		25%	3500	-
3 Cleaners		25%	1500	
		Sub Total	11,000	-

2. Supplies and Materials

	Taka
HCT & Specific Gravity 100X3 = 300 specimen @ Tk.9.30	2790
Electrolytes 100 X 3 = 300 specimens @ Tk. 12	3600
Stool M/E 100 speciemns @ Tk. 2.50	250
Stool culture 100 specimens @ Tk.25	2500
Stool ELISA TEST 50 specimens @ Tk. 30	1500
LT/ST Test 100 specimens @ Tk 5	1500
ORS Packets 300 @ Tk 2	600
Sub Total	12,740

3. Equipments — Nil

4. Hospitalization 100 X 2.5 X 150 — 37,500

5. Oltpatient — Nil

6. Transport — Nil

7. Travel — Nil

8. Transport of Things — Nil

		Taka	Dollar
9.	Rent	Nil	
10.	Printing: Forms	2000	
	Publications		200
	Total	63,240	200

Incremental cost excluding Personnel salary — Tk. 52,240 — Dollar 200

Total Incremental cost — Tk. 52,240 — Dollar 200

= US $ 2612

(Conversion rate US $ 1 = 20)

Grand Total = US $ 2612 + US $ 200

= US $ 2812

BUDGET SUMMARY

		Taka	Dollar
1.	Personnel	11,000	-
2.	Supplies	12,740	-
3.	Equipments	-	-
4.	Hospitalization	37,500	-
5.	Outpatient	-	-
6.	Transport	-	-
7.	Travel	-	-
8.	Transport of Things	-	-
9.	Rent	-	-
10.	Printing	2,000	200
11.	Contractual service	-	-
12.	Construction	-	-
	Total	63,240	200
	Total Incremental cost excluding personnel salary	52,240 US $ 2612	200 200

Grand Total = US $ 2812

BIBLIOGRAPHY

1. Clinical Management of acute diarrhoea WHO/DDC/79.3.

2. Hirschorn, N., Kinzi, J.L., Sachar, D.B., Northrup, R.S., Taylor J.O., Ahmad, S.A. & Philips, R.A. (1968) Decrease in net stool output in cholera during intestinal perfusion with glucose containing solutions. N. Eng. J. Med. 279, 176-181.

3. Nalin, D.R., Cash, R.A., Islam, R., Molla, M. & Philips, R.A. (1968) Oral maintenance therapy for cholera in adults. Lancet II, 370-373.

4. Cash, R.A., Nalin, D.R., Rochat, R., Reller, L.B., Haque, Z.A. & Rahman, A.D.M.M. (1970a) A clinical trial of oral therapy in a rural cholera treatment center. Am. J. Trop. Med. Hyg. 19, 653-656.

5. Cash. R.A., Nalin, D.R., Forrest, J.N. & Abrutyn, E. (1970) Rapid correction of acidosis and dehydration of cholera with oral electrolyte and glucose solution. Lancet 2, 549-550.

6. Mahalababis, D., Chowdhuri, A.B., Bagchi, N.G., Bhattacharja, A.K., and Simpson, T.W.: Oral fluid therapy of cholera among Bangladeshi Refugees, Johns Hopkins Med J 132 : 197-205, 1973.

7. Kielmann, A.A. and McCord, C., Home treatment of childhood diarrhoea in Pubjab village, J. Trop. Paed. Environ. Child Health 23 : 197-201, 1977.

8. "Control of Diarrhoeal Diseases: WHO's Programme Takes shape" WHO Chronicle 32 : 369-372, 1978.

9. Nalin, D.R. Hirschorn, N.: Research on Oral Rehydration Therapy for Diarrhoeal Dehydration. Regional Planning Meeting on Diarrhoeal Disease Control. WPR/BVD (DDC)/ 79.6, June 4, 1979.

10. "Clinical Management of Acute Diarrhoea, Report of a Scientific Working Group (New Delhi), WHO/DDC/79.3 Oct-Nov. 1978.

11. Islam, M.R. et al: Use of base precursors as a substitute of bicarbonate in the oral rehydration solution (to be published)

12. Draft of the Package Leaflet of "SERVIDRAT" supplied by Ciba-Geigy Limited.

ABSTRACT SUMMARY

1. 50 adult (15-50 yrs) and 50 children (under 5 yrs) suffering from acute watery diarrhoea having moderate dehydration attending the outpatient department of ICDDR,B will be selected for study. Patient's with complications e.g., fever, pneumonia and convulsion will be excluded from study.

2. There is no potential risk involved in the study.

3. Not applicable

4. All records will be kept strictly confidential. They will remain with the Principal Investigator. If data is put on computer tapes, study patients will be referred to by number only.

5. Informed consent (signed or thumbimpression) will be obtained from all the guardians of the patients. There is no procedure in the study which may unmask the privacy of the subject.

6. Interview will be taken only related to the history of illness and is needed only for clinical management of the disease. 5 minutes will be enough to take such a clinical history.

7. The patients will gain through treatment of their illness.

8. The study will require blood and stool only.

CONSENT FORM

The ICDDR,B is carrying out research to develop most economic and effective way to treat diarrhoea in a simple way like, oral saline. We will try an ORS in Tablet form in comparison to the presently available ORS in powdered form. This has a pleasant flavour and has no serious side effects. We want to see whether the tablet form is better than the powdered form or not. We would like you to participate in this study for the benefit of sodiety. If you/your child participate in the study, you can expect that:

1. You/your child will be given best possible care

2. It will be necessary to stay for atleast 2 days or more until diarrhoea stops.

3. While you/your child will be in hospital, we will test a total of 3 samples of blood (about 2 c.c. each time) to know the condition of the disease. These will be routine tests.

4. If the oral saline gaiven to you/your child fails by any chances, you/your child will be taken off from the study and will be treated with proper intravenous fluid.

If you do not like to participate in the study at any stage, you will still be treated like others in this hospital.

If you are voluntarily willing to participate in the study, then please sign your name or give left thumb impression below.

Signature of Investigator

Signature of LTI of legal guardian of the child

Date: _____