Attachment 1.

Date 16.9.81.

ETHICAL REVIEW COMMITTEE, ICDDR,B.

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

Application No. 81-040 Supporting Agency (if Non-ICDDR,B) _____

Title of Study The efficacy of ORS in correcting Hypokalaemia due to Acute Dehydrating Diarrhoea in Children (Under 5 yrs of age)

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

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

1. Source of Population:
   (a) Ill subjects — (Yes) No
   (b) Non-ill subjects — Yes (No)
   (c) Minors or persons under guardianship — (Yes) No
2. Does the study involve:
   (a) Physical risks to the subjects — Yes (No)
   (b) Social Risks — Yes (No)
   (c) Psychological risks to subjects — Yes (No)
   (d) Discomfort to subjects — (Yes) No
   (e) Invasion of privacy — Yes (No)
   (f) Disclosure of information damaging to subject or others — Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) — (Yes) No
   (b) Use of fetal tissue or abortus — Yes (No)
   (c) Use of organs or body fluids — (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study — (Yes) No
   (b) Procedures to be followed including alternatives used — (Yes) No
   (c) Physical risks — (Yes) No
   (d) Sensitive questions — (Yes) No
   (e) Benefits to be derived — (Yes) No
   (f) Right to refuse to participate or to withdraw from study — (Yes) No
   (g) Confidential handling of data — (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — Yes (No)
5. Will signed consent form be required:
   (a) From subjects — Yes (No)
   (b) From parent or guardian (if subjects are minors) — (Yes) No
6. Will precautions be taken to protect anonymity of subjects — (Yes) No
7. Check documents being submitted herewith to Committee:
   - 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)
   - NA 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.

Principal Investigator 16/9

Trainee

81-040
Recd 25/9/81

SECTION 1 - RESEARCH PROTOCOL

1. TITLE: The Efficacy of ORS in correcting Hypokalaemia due to Acute Dehydrating Diarrhoea in Children under 5 years of age.

2. PRINCIPAL INVESTIGATOR: Dr. Syed Masud Ahmed

CO-INVESTIGATORS: Dr. Rafiqul Islam
Dr. Mominul Alam

3. STARTING DATE: September 1, 1981

4. COMPLETION DATE: March 1, 1982

5. TOTAL DIRECT COST:

6. SCIENTIFIC PROGRAMME HEAD:

This protocol has been approved by the Pathogenesis and Therapy Working Group.

Signature of Scientific Program Head: [signature]

Date: 16/9/1981

7. ABSTRACT SUMMARY:

One of the most important advances in the field of diarrhoeal disease research has been the discovery that dehydration in cases

of acute diarrhoea of any etiology and in all age groups can be treated orally. Even in the presence of copious diarrhoea, the Oral Rehydration Solution (ORS) is absorbed in the small intestine, thus replacing the acute diarrhoeal losses. Recent experience with the use of oral fluid therapy in many developing country resulted in significant reductions in diarrhoea mortality and also morbidity. Since then this health intervention programme has been recognized as one of the major way to substantially reduce infant and child deaths around the world. The present ORS recommended by WHO was originally devised for adults. But recently questions has arised regarding the efficacy of this soln, in correcting hypokalaemia in children, since stool electrolyte losses in children differs significantly from adults.

A clinical study is proposed to find the efficacy of ORS to correct hypokalaemia in Bangladeshi children under five years age. 100 children with acute watery diarrhoea and mild to moderate dehydration will be taken into the study. After history taking and brief physical exam. weight and 2 c.c. of venous of blood will be taken form the patients prior to therapy with ORS. Patients requiring intravenous fluid will be discarbed from the study.

There will be no dietary restriction. Banana, Dub and other fruits and foods containing high potassium will not be allowed. Patients will be discharged when they pass soft stool or have had two consecutive 8 hrs. period with less than 5 ml/kg/8hrs of liquid or water stool. 2cc of venous blood will be collected at 24 hrs and at the time of discharge, after clinical cure, together with weight and these will be compared to see the efficacy of ORS in correcting initial deficit of potassium.

8. REVIEWS:

(a) Research involving human subjects.

(b) Research committee

(c) Director

(d) BMRC

(g) Controller/Administrator

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objectives:

The objectives of this study is to find out the efficacy of WHO recommended ORS in correcting hypokalaemia due to acute dehydrating diarrhoeas in children under five years of age will be observed.

2. Background:

Diarrhoeal disease continue to be the major cause of morbidity and mortality in children under five years of age throughout the less developed areas of the world. In Latin America, one study examined 33826 infant and childhood deaths and 30% were attributed to Diarrhoea (Puffer & Serrano 1973)[1]. In Guatemala, India and Indonesia careful prospertive field studies showed a mean of 100 to 200 attacks of diarrhoea per 100 children that is one to two attacks per child per year during the first 3 years of life and a death rate of 20-55 per 1000 children annually (Van Ziji et al)[2]. In a long term field study in the Guatemalan Indian village of Santa Maria Canque (Mata et al, 1978) diarrhoea was the commonest disease in first 3 years of life accounting for 43% of all diseases and disabilities and the diarrhoeal rate was about 8 episodes per child per year.

According to Data for Bangladesh in 1975 there were 23.9 death per thousand population and diarrhoea was responsible for 34% of these deaths, thus the most common cause.[3]

Diarrhoea causes death acutely due to large scale losses of water and electrolytes from the body beyond tolerable limits, i.e., dehydration and the principle of treatment is to replace the lost substances until the body gets rid of the harmful agent. From the observation that glucose stimulated sodium absorption remained normal in cholera (Hirschorn et al 1968)[4] 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 (Nalin et al 1968)[5]. It was later proved that not only can oral glucose - electrolyte solutions adequately maintain hydration in the face of continuing diarrhoeal losses (Cash et al. 1970a)[6], but also, if given early in the course of illness, can entirely obviate the need for intravenous fluids (Cash et al 1970b)[7]. Recent experience with the use of oral fluid therapy in many developing country settings resulting in significant reductions in diarrhoea mortality [8,9,10,11,12] 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 Oral Rehydration Solution (ORS) was initally devised for cholera patients especially, adults. But the amount of electrolytes lost in the stool of adult and children differ significantly. The cholera stool of child contains less Na and more K than the stool of the adult[13] (Table).

Table. Composition of cholera stools in adults and children:

Cholera stool (average values)	Concentration, mEq/L			
	Na^+	K^+	Cl^-	HCO_3
1. Adult	135	15	100	45
2. Children	105	25	90	30

Potassium losses from acute diarrhoea can be particularly harmful in infants, especially those that are undernourished. Potassium absorption takes place passively depending on the concentration gradient, i.e., a potassium concentration higher than that in plasma will induce absorption. Thus the children require significantly more K than adults and treatment with present form of ORS may not correct hypokalaemia in cholera and related acute dehydrating diarrhoeas. Repeated therapy of children, especially malnourished ones, with oral solutions containing inadequate K will certainly lead to increased risk of massive total body potassium depletion during acute diarrhoeal attacks, with associated increased risk of muscle weakness, arrhythmias, ileus and hypokalaemia nephropathy.[14] Nalin et al in a recent study showed that ORS with 90 mEq/L of Na is safe and effective in infants and children but is occassionaly associated with transient hypernatraemia which can be avoided by allowing extra plain water. On the other hand, the 20 mEq/L of K in ORS failed to correct hypokalaemia in this age group and he

showed that hypokalaemia after therapy can be eliminated using 35 mEq/L of K^{14}.

3. Rationale:

Paediatric diarrhoea is one of the major causes of death in Bangladesh. The ORS recommended by WHO which was originally devised for adult cholera patients contain more sodium and less potassium than the stool electrolyte loss of the children. Solutions containing less K may fail to correct the hypokalaemia in infants and children. This become especially important in chronic malnourished children, whose total body potassium is already at a low ebbe, and who suffers several episodes of diarrhoea per year. Treatment with ORS may fail to correct hypokalamia in these vulnerable group of patients. There is not much study on the efficacy of ORS in correcting hypokalaemia in the infants and children. This study will find out whether ORS can correct the hypokalaemia in children under five years of age, so that future prospective study could be undertaken with ORS containing different concentrations of K or extra K^{-} supplementation in the from of locally available fruit.

B. SPECIFIC AIMS

(1) To find out the efficacy of ORS in correcting hypokalaemia in children under five years of age.

C. METHODS AND PROCEDURES

1. Subjects: 100 patients under five years of age with history of acute watery diarrhoea of less than 24 hrs duration and judged clinically mild and moderately dehydrated & who will still be able to tolerate oral fluid will be selected for the study. Patients will be excluded from the study if they have received antibiotics withing a week prior to hospitalizations, have complications such as fever, pneumonia, meningitis, fever etc. or are severely malnourished. Also the patients with failure of oral therapy and in need of I.V. fluid in any stage of study will be excluded. The patients will be kept in T.C. The patients will be selected each morning 3 at a time fulfilling the above criteria and will be requested to participate in the study.

The parents of the children will be informed of the study and if they agree to participate they will be included in the study.

2. Clinical procedures:

Selected patients will be briefly examined by the physician to exclude any complications e.g. bronchopheumonia, meningitis etc. Then the patient will be weighed and 2 cc of venous blood will be taken for the measurement of Na, K and Sp. gr & Bicarb. Then oral therapy will be started and a 8 hourly input-output chart will be maintained. No intravenous fluid will be administered. Initial

rehydration as well as subsequent maintenance of hydration status will be done with ORS. Patient will be given oral fluid ad lib to drink as long as diarrhoea persists. Breast milk and free water will be allowed and there will be no dietary restrictions, Except fruits containing high potassium such as banana, Dub etc.

The patients will be clinically evaluated 8 hourly which will include examinations for skin turger, mucous membrane, eye signs, pulse volume, signs of pul oedema.

Any patient with failure to rehydrate or maintain with oral fluid will be treated appropriately with I.V. Fluid and will be excluded from the study. Patient will be discharged when they pass soft stool or have had two consecutive 8 hour periods with less than 5 ml/kg/8hr of liquid or water stool. At 24 hrs and at the time of discharge 2cc of venous blood will be taken for Na, K & Sp. gr. & Bicarb. A summary of clinical measurements is as follows:

	Adm.	4hr	8hr	16hr	24hr	48hr	Discharge
Clinical Evaluation	x	x	x	x	x	x	x
Weight	x		x		x	x	x
Intake	x		x		x	x	x
Output	x		x		x	x	x
Sp. gr.	x				x	x	x
Serum Na & K & HCO_3^-	x				x	x	x

3. Analysis of Data: All the information will be kept in a flowsheet for each patient. Analysis will be straight forward. Admission wt. sp. gr. and electrolytes will be compared with 24 hr. 48hr and discharge wt. Sp. gr. and electrolytes after adequate correction of fluid loss and tests will be done for statistical significance (Students' t test). Also the amount of oral fluid taken and its correlation with correction of hypokalaemia will be compared.

D. SIGNIFICANCE: From be result of this study, it will be possible to determine whether present WHO/UNICEF recommended ORS alone is sufficiento correct hypokalaemia due to acute watery diarrhoea of any aetiology in Bangladeshi children under five years of age.

E. FACILITIES REQUIRED

1. No new office space is required.
2. Laboratory facilities for routine Biochemistry will be utilized.
3. No new lab space is required.
4. Hospital support - The space in T.C. will be utilized for patient hospitalization.
5. Logistical support - None.
6. Major items of equipment - No new item is required.
7. Other - None.

F. COLLABORATIVE ARRANGEMENT - NIl.

BIBLIOGRAPHY

1. Puffer, R.R. & Serrano, C.V. (1973) Patterns of mortality in Childhood. PAN AM. HEALTH ORBAN. Sci. Publ No. 262.

2. Van Zijl, W.J. (1966) Studies on diarrhoeal diseases in seven countries by the WHO diarrhoeal disease advisory team. Bull, W.H.O. 35, 249-261.

3. Bangladesh Health Profile 1977 published by Health Information Unit, Ministry of Health and Population Control (Health Div). 1978.

4. Hirschhorn, N., Kinzi, J.L., Sachar, D.B. Northrump, 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.

5. Nalin, D.R., Cash, R.A., Islam, R., Molla, M. & Philips, R.A. (1968) Oral maintenance therapy for cholera in adults. Lancet 2, 370-373.

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

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

8. Mahalanabis, D, Choudhuri, 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.

9. Kielmann, A.A. and McCord, C., Home treatment of Childhood Diarrhoea in Punjab village, J. Trop. Paed. Environ. Child Health 23:197-201, 1977.

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

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

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

13. Greenough, William B., III, Principles and prospects in the Treatment of Cholera and Related Dehydrating Diarrhoeas: Cholera and Related Diarrhoeas. 43rd Nobl Symp. Stockholm 1978, 211-218 (Krager, Basel 1980).

14. Levinsky, Norman G., Fluids and Electrolytes: Harrison's Principles of Internal Medicine 9th ed., McGraw-Hill Book Company:

SECTION III - BUDGET

DETAILED BUDGET:

1. Personnel Services:

Name	Position	% of effort	Project Taka	Requirement Dollar
Dr. Syed Masud Ahmed	Principal Investigator	50%	4,500	-
Dr. M.R. Islam	Co-Investigator	5%	2,600	-
Dr. M. Alam	"	10%	1,000	-
3 Staff Nurse		25%	6,894	-

2. Supplies & Materials:

Hct & Sp. gr. exam 400 specimens	800
Electrolytes exam 400 specimens @ 20 taka	8,000

3. Equipment - Nil

4. Hospitalization - Nil

5. Outpatient - 100 patients x 3 days/pt. 6,000

6. Transport - Nil

7. Travel - Nil

8. Transport of things - Nil

9. Rent - Nil -

10. Printing: Forms & Publications 5,000

11. Contractual service - Nil

12. Construction - Nil

SECTION III - BUDGET

Budget Summary	Taka	Dollar
1. Personnel	14,994	-
2. Supplies	8,800	-
3. Equipments	-	-
4. Hospitalization	-	-
5. Outpatient	6,000	-
6. Transport	-	-
7. Travel	-	-
8. Transport of things	-	-
9. Rent	-	-
10. Printing	5,000	-
11. Contractual services	-	-
12. Construction	-	-
Total:	34,794	-
30% Overhead	10,438	
	45,232	3015.47

Conversion $ 1 = Tk. 15

Grand Total = $ 3016

ABSTRACT SUMMARY

1. One hundred Bangladeshi children under 5 years of age suffering fromacute dehydrating diarrhoea attending the out patient clinic of ICDDR,B at Dacca will be taken in this 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 (singed or thumbimpression) will be obtained from all the guardians of the patients. There is no procedure in this study which may unmark 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. 3 minutes will be enough to take such a clinical history.

7. The child will gain through treatment of his illness. Society will gain if correct concentration of potassium in ORS can be scrutinized.

8. They study will require examination of blood only.

CONSENT FORM

The ICDDR,B Bangladesh is carrying out research to treat diarrhoea in a very simple way like oral rehydration therapy. For this purpose the formula recommended by WHO is used. This formula was originally designed for adults. But the electrolytes loss in the stool is not same in adults and children. Children loss more potassium in the stool than the adults. We like to know whether the present composition of ORS can correct potassium loss in the stool in children under 5 yrs of age. We like your children to participate in the study for the well being of mankind.

If you decide to participate in our study, you can expect that

(1) Your child will be given best possible care for diarrhoea.

(2) Your child will be needed to stay at least 2/3 days or even more until your diarrhoea stops.

(3) While you are in hospital, we want to test total of 2+ samples of blood (about 2cc each time) to know serum electrolytes. This is taken routinely in our inpatient departments.

(4) If ORS fails to treat by any chances your child will be taken off from the study and will be treated with proper intravenous fluid.

(5) If you do not like to participate in the study, still you will be treated like others in this hospital.

(6) Besides, if you wish you are at liberty to withdraw from the study at any time without any obligations and jeoperdizing your medical care and treatment.

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

Signature of Investigator

Date: _____

Signature _____

or LTI of the Legal Guardian of the child.

Date: _____

HYPOKALAEMIA STUDY

DATE: _____

TIENT'S NAME _____ AGE: _____ SEX _____ TC NO. _____

ime / rs.	Wt (kg)	Skin* Turgor	Dehydration**	Pulse /min	Resp. /min	Fluid Intake (ml)		Stool (ml)		Urine (ml)	HCT. %	Sp. gr.	Serum Electroly		
						ORS	Pl.water & milk	Volume	Colour & Consistency				Na	K	CO_2

* 0=Normal, 1=Fiar, 2=Poor

** 0=None, 1=Mild, 2=Moderate, 3=Moderate to sever, 4=Severe.

সম্মতি পত্র

আন্তর্জাতিক উদরাময় গবেষনাকেন্দ্র উদরাময় চিকিৎসার জন্য খাওয়ার স্যালাইনের মত সহজ পদ্ধতি দ্বারা চিকিৎসার জন্য গবেষনা চালিয়ে যাচ্ছে। এই চিকিৎসায় WHO অনুমোদিত খাওয়ার স্যালাইন ব্যবহার করা হয়। এই ফরমুলা প্রথমে পূর্নবয়স্কদের জন্য আবিষ্কার করা হয়েছিল। কিন্তু মলে ইলেকট্রোলাইট এর পরিমান পূর্নবয়স্ক এবং শিশুদের ক্ষেত্রে এক নয়। শিশুদের মলে নিতি পটাশিয়ামের পরিমান পূর্নবয়স্কদের চেয়ে বেশী। আমরা জানতে চাই বর্তমান WHO অনুমোদিত খাওয়ার স্যালাইনে যে পরিমান পটাশিয়াম আছে তা ৫ বছর বয়সের নীচে শিশুদের পটাশিয়াম ঘাটতি পূরন করতে পারে কি না। আমরা চাই মানবতার বৃহত্ত স্বার্থে এই গবেষনায় আপনার শিশুর অংশ গ্রহন করুক।

আপনি যদি গবেষনায় অংশগ্রহন করতে চান, তবে,

১। উদরাময় চিকিৎসার জন্য সর্বোত্তম ব্যবস্থা নেয়া হবে

২। আপনার শিশুকে ২/৩ দিন কিংবা পায়খানা ভাল না হওয়া পর্যন্ত থাকতে হবে।

৩। এই সময়ে আমরা চারবার রক্তপরীক্ষার জন্য (প্রতিবারে মাত্র দুই মিলি) নেব। আমাদের ইতোরে রক্তের পরীক্ষার জন্য নিয়মিত এই পরিমান রক্ত নেই

৪। যদি খাওয়ার স্যালাইনে আপনার শিশু ভাল না হয়, তবে গবেষনা থেকে তাকে বাদ দেয়া হবে এবং রক্তে স্যালাইন দিয়ে চিকিৎসা করা হবে।

৫। আপনি গবেষনায় অংশগ্রহন করতে না চাইলেও চিকিৎসার কোন ত্রুটি হবে না।

৬। এছাড়াও, যে কোন সময়ে গবেষনা থেকে নাম প্রত্যাহারের স্বাধীনতা আপনার থাকবে।

আপনি যদি স্বেচ্ছায় গবেষনায় অংশগ্রহনে

বাকী থাকেন তবে না
বাম বুড়া আঙ্গুলের ছাপ দিন

গবেষকের স্বাক্ষর

তারিখ

কেসার অভিভাবকের
স্বাক্ষর/টিপসহি

তারিখ