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## SECTION I - RESEARCH PROTOCOL

1) Title: Sucrose vs. Glocuse Electrolyte Oral Solution - In the Diarrhea of Infants.

2) Principle Investigator: David A. Sack, M.D.

3) Starting Date: July, 1977

4) Completion Date: December, 1978

5) Total Direct Cost:

6) Abstract Summary: (250 words or less)

We plan a doubleblind trial to determine the effectiveness of an oral glucose electrolyte solution (WHO solution) in the hydration of infants with rotavirus diarrhea and to compare sucrose electrolyte solution with glucose electrolyte solution as oral hydration therapy in infants with diarrheal diseases of all etiologies in Bangladesh. Approximately 300 children, aged 3 months to 4 years will be admitted into the study during 8 to 12 months in order to obtain a representative sample of all etiologic agents causing diarrhea in infants many of which are seasonal. The primary determinant of failure of a treatment will be the need to begin (or - resume) I.V. Hydration; however, other factors including mal-absorption of sugars and patient's acceptance of therapy will also be examined.

7) Reviews: (leave blank)

a) Research Involving Human Subjects:_____

b) Research Committee:_____

c) Director:_____

d) BMRC:_____

e) Controller/Administrator:_____

## SECTION II - RESEARCH PLAN

### A. INTRODUCTION

1. Objective: To help eliminate morbidity and mortality resulting from diarrheal disease in infants by developing effective, economical oral hydration fluid.

2. Background: The complications and mortality resulting from syndromes of watery diarrhea are almost exclusively limited to those of dehydration. The primary therapy therefore in the watery diarrhea syndromes is that of rehydration and maintenance hydration. In severe diarrheal states this can only be accomplished with intravenous fluids; however, most diarrheal episodes can be managed successfully with oral therapy. Documentation of the effectiveness of oral GE solution has been established in Calcutta, Dacca as well as in the United States, in both cholera and non-cholera diarrhea.

   The rationale for using an oral electrolyte-solution is as follows: In cholera and E.coli diarrhea the diarrhea results from an activation of cyclic AMP with resulting massive outpouring of fluids and electrolytes from the mucosal cells of the small bowel. Absorption however, remains normal throughout the small intestine.

   There are three primary modalities through which electrolyte and water are absorbed by the small intestine:

   1) the sodium pump system which carries water along with sodium.
   2) Passive absorption of water.
   3) Glucose facilitated absorption.

   It is this glucose facilitated absorption which is utilized in the oral glucose-electrolyte rehydration therapy.

The advantages of oral solution for the treatment of watery diarrheal syndromes are several:

1) The volume of sterile intravenous solution is greatly decreased. This is of very particular importance in the areas where intravenous solutions are limited either by facilities or by economic considerations.

2) Intravenous solutions may be avoided altogether in some patients thus avoiding complications of intravenous infusions.

3) This may be a very practical form of therapy in which hydration can be carried out in the home without the use of hospitals and it is especially useful in epidemics of watery diarrhea where logistics prohibits wide use of intravenous solutions.

Although the oral glucose electrolyte solution has been documented to be effective in both cholera and non-cholera diarrhea, the experience with this solution has been primarily carried out in patients above the age of two years. The epidemiology of watery diarrheal syndromes however, is that infants less than three years of age are the persons who are at highest risk of diarrheal disease. In many parts of the world the etiologic agent responsible for the watery diarrheal syndrome in this age group has been shown to be the rota-virus. This virus has also been demonstrated in Bangladesh, however, the relative importance of this pathogen has not yet been established here. The pathogenesis of rota-virus infection, unlike cholera or E.coli, does involve invasion of mucosal cells by the pathogen. We cannot assume therefore, that the absorption, especially the glucose facilitated absorption, is normal in the rota-virus infection as it is in E.coli

and cholera diarrhea. In fact, absorption of d-xylose and lactose have been found to be abnormal in infections of the Norwalk agent, another viral diarrhea. It is therefore necessary to establish the efficacy of the GE solution in diarrhea caused by rota-virus.

Recently a study was carried out in Dacca comparing the effectiveness of the sucrose-electrolyte solution with the glucose-electrolyte solution in patients over the age of six years with watery diarrhea. In this study the two solutions were shown to be equally effective. However, because of the age group studied in this previous protocol, we do not have information on the efficacy of the sucrose-electrolyte solution in infants especially those infants with rota-virus infection.

In order for sucrose-solution to be effective the sucrose must first be hydrolized by a sucrase in the small intestine, thereby releasing free glucose and fructose. Glucose is then utilized in the glucose facilitated transport. It is known however, that diarrheal syndromes are often associated with a temporary decrease in disaccharidase levels in the small intestine; therefore, it is possible that sucrose would not be effective especially in rota-virus. The importance of this question is a very practical one; since in many countries of the world, glucose is not available, while sucrose is nearly always available. In those situations where glucose is not available; sucrose, if effective, would be very useful in the oral hydration therapy solution.

Several technological advances in the last few years have made the study possible at this time, where it was not possible earlier. These

advances consist primarily of the ability to detect the rota-virus antigen as well as E.coli heat labile toxin by means of an enzyme linked immunosorbent (Elisa). This assay now makes possible the study of large numbers of cases of diarrhea while determining the responsible etiologic agent.

3. Rationale: It is necessary to determine the efficacy of both GE and SE in the diarrhea of infants with respect to etiologic diagnosis so that a decision can be formulated as to the adequacy and limitations of these solutions as oral hydration solutions in this age group.

B. SPECIFIC AIMS

1. To determine the efficacy of GE in the hydration therapy of infants less than four years of age with rota-virus diarrhea.

2. Compare the effectiveness of a SE with GE in the hydration of patients with diarrhea due to rota-virus, cholera and E.coli as well as diarrhea of unknown etiology.

C. METHODS OF PROCEDURE

1. Patient population. A sample of patients - 3 months to four years of age, weighing 4 Kg being admitted to the Cholera Hospital because of uncomplicated acute watery diarrhea (1 week) who have not received previous antibiotic during last two weeks and whose parents have given informed consent will be studied. Because some of the diseases which will be studied are seasonal, we will need to sample patients over a long period of time in order to have adequate numbers

of patients with rota-virus, cholera and E.coli diarrhea. We plan therefore, to admit patients to the study during the first week of each month beginning in August 1977. During the study week we will accept the first 5 patients admitted to the hospital each day who meet the above criteria. Patients to be admitted to the study will be transferred to the study ward.

Clinical Information. All patients will receive a standardized physical examination including an admission weight. Physical examination will note specifically signs of dehydration. Blood will be drawn for a CBC, electrolytes, blood sugar, creatinine, specific gravity, and an acute sera for antibody determination. A stool specimen will be obtained for culture, for microscopic examination, for sodium and potassium determination, for sugar determination, and two alequates of stool will be frozen (to be examined for rota-virus antigen and heat-labile enterotoxin). Urine will be obtained for routine urinalysis, for sodium, potassium, osmolality and specific gravity.

Treatment of Patients. Each child will be stratified as to the clinical degree of dehydration (mild, moderate or severe) and randomized in a double blind manner to one of two treatment groups.

Group I (Glucose-Electrolyte Solution) will be treated as follows. The initial replacement therapy for patients who are severely dehydrated will be by intravenous fluid using standard I.V. solutions (70 ml/Kg as quickly as possible). The I.V. will then be removed. Oral fluid will begin when tolerated to complete the rehydration (30 ml/Kg).

Initial hydration for moderately dehydrated patients will be with oral fluid alone (70 ml/Kg over 4-6 period). Mildly dehydrated patients will be given oral fluid 50 ml/Kg over 6 hours.

Maintenance Therapy of Group I will be by oral hydration using GE to replace stool on an approximately one to one basis, volume for volume. Stool passed during the initial rehydration period will also be replaced during this time.

Group II (Sucrose-Electrolyte Solution) will be treated exactly as Group I except that sucrose will be substituted for glucose in this solution.

Fluids to be used will be as follows:

| Glucose Electrolyte Solution | Sucrose Electrolyte Solution |
|---|---|
| $Na^+$ 90 meq/liter | $Na^+$ 90 meq/liter |
| $K^+$ 20 meq/liter | $K^+$ 20 meq/liter |
| $Cl^-$ 80 meq/liter | $Cl^-$ 80 meq/liter |
| $HCO_3$ 30 meq/liter | $HCO_3$ 30 meq/liter |
| Glucose 111 mM/liter | Sucrose 111 mM/liter |
| which is made by: | which is made by: |
| NaCl 3.5g/liter | NaCl 3.5g/liter |
| $NaHCO_3$ 2.5g/liter | $NaCHO_3$ 2.5g/liter |
| KCl 1.5g/liter | KCl 1.5g/liter |
| Glucose 20g/liter | Sucrose 40g/liter |

Follow up evaluations will be made as shown on the enclosed chart.

Maintenance replacement therapy will continue until the diarrhea stops.

This is defined as a 24-hour period during which no watery stool has been passed. Oral feedings may begin at 12 hours including continuation of breastfeeding.

Antibiotics will not be used unless specifically indicated. Intake and output records will be maintained on a 4 hourly basis during the first 4 hours, then every 8 hours using cholera cots or ileostomy bags. If children are vomiting, oral fluids will be given by small amounts frequently; however, nasogastric tubes will not be used for vomiting. They may be used however, to allow patients to sleep if necessary. All oral intake will consist of the oral solution until the feeding is started at which time water will be available ad lib. Patients will be discharged roughly twenty-fours hours after diarrhea stops.

The need to resume intravenous fluids will be judged as a failure for the oral solution. Decision to resume intravenous fluids will be based on objective criteria: 1) a return of clinical signs of dehydration including loss of body weight. 2) Persistent vomiting preventing the use of oral fluid. 3) an increase in plasma specific gravity ($>1.030$). If patients are restarted on intravenous fluids, after rehydration they will again be tried on the oral-electrolyte solution which they have previously received.

If electrolyte imbalance develops during therapy ($Na<125$, $>155$; $K<2.5$, $>6.0$) patients will be discontinued from the study and considered a treatment failure.

Patients will be asked to return 10-14 days after discharge for repeat serum specimen.

Special Lab. Studies:

Microbiology - E.coli from the admission stool culture will be tested for heat labile enterotoxin using the adrenal cell assay (or Elisa assay), and for heat stable toxin using the infant mouse assay. Antibodies to heat labile toxin will be determined by the microtiter adrenal neutralization assay.

Rota-virus antigen from stool will be determined using an Elisa assay. Antibodies to rota-virus will be determined using a complement fixation test.

Biochemistry - Stool sugars will be determined by measuring reducing substances in the stool, before and after hydrolysis, using clinitest tablets.

After the study is compl ted it should be possible to compare the sucrose with the glucose groups as follows:

1) Admission values: objective evidence of the severity of the disease should be same in both groups. Pathogens isolated from both groups should be the same.

2) Failure of oral fluids: defined as necessitating return to intravenous fluids or dropping patient from study because of electrolyte abnormality.

3) Duration of diarrhea.

4) The volume of diarrheal stool.

5) The amount of fluids given, both intravenous and oral.

6) Any adverse reactions during therapy.

7) Ease of fluid administration, including acceptance of oral fluid by patients.

Because many of the etiologic agents causing watery diarrhea are seasonal in nature this study will need to be carried out over an 8 to 12 months time period, or until there are 50 patients in each of the diagnostic categories (rotavirus, cholera, E.coli) treated with each oral fluid regiment.

Randomization to either GE or SE will be done in a double blind manner. Mr. Akbar Ali, Biochemistry Branch Chief, will prepare the two solutions and mark one solution "A" the other "B", for each one week treatment period. The code for "A" and "B" will be changed randomly between treatment periods. Prospective stratification of patients will be by degree of dehydration; however, stratification by etiologic agent will be by restrospective analysis. The data will be transferred to IBM cards for data storage and analysis.

D. SIGNIFICANCE

From the results of this study, it should be possible to determine the efficacy of the sucrose-electrolyte solution in the treatment of watery diarrhea, and to determine the efficacy of both glucose and sucrose electrolyte solutions in rota-virus diarrhea. This is important in the treatment of watery diarrheal syndromes throughout the world, especially in rural or under-developed countries where medical facilities are limited.

E. FACILITIES REQUIRED

1) Office for principle investigator. Office for study ward physicians in the ward area.

2) Laboratory space: the routine bacteriology, biochemistry and immunology laboratories will be utilized. In addition one laboratory will be necessary for the development of the Elisa assay for rota-virus and for testing of specimens for rota-virus and enterotoxigenic E.coli heat labile toxin. (See protocol Seaton, et. al. Development of Elisa).

3) Hospital Resources - the study ward will be used. Maximum of 35 hospital beds will be used during each study period. A seven day study period will occur during the first week of each month beginning on a Tuesday. Study physicians will need to be present on the ward 24 hours per day during each study period to admit new patients and monitor therapy. A study nurse will be necessary 24 hours/day during the study periods.

It should be noted that these patients would be hospitalized regardless of the study, and no "extra" patient days are planned.

4) Animal Resources - E.coli from approximately 300 specimens will be tested for heat stable toxin which will require approximately 5400 infant mice.

5) Logistical Support - We will need assistance from the epidemiology Branch to help secure the convalescent serum specimen. Also 4 hours of computer time is anticipated.

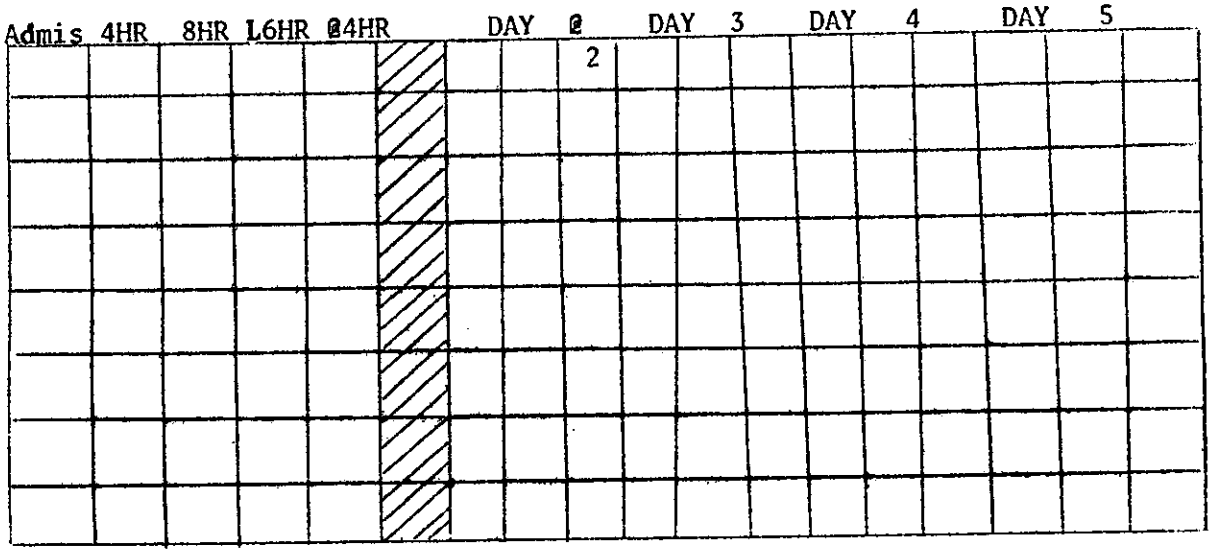
6) Major items of equipment - A colorimeter suitable for microtiter plates will be needed in this study. This is included in a separate protocol.

7) Other specialized requirements - The two oral solutions will be prepared by biochemistry branch.

Name_____ Hosp. No._____ StudyNo._____ Date of Admn._____

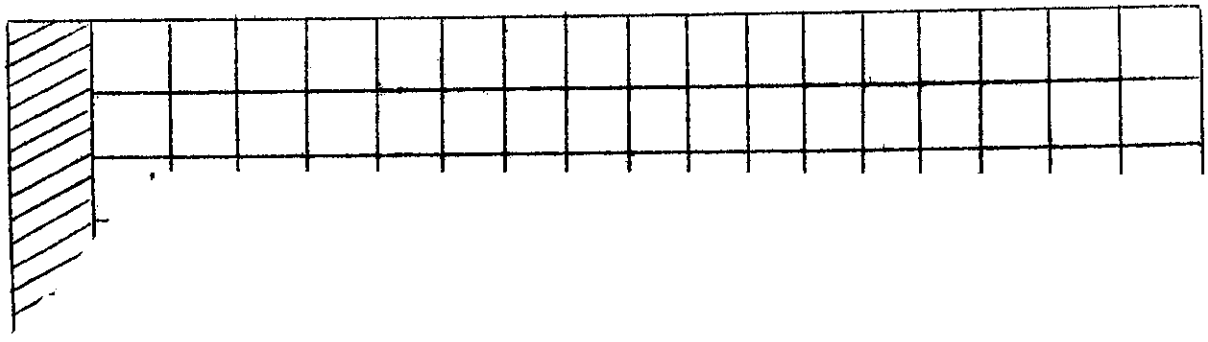
Oral Fluid A B (circle one)

## Clinical Flow Sheet




* 0 - Normal, 1 - mildly dehydrated, 2 - severely dehydrated, 3 - overly dehydrated.

** 0 - readily accepts fluids, 1 - accepts reluctantly, 2 - will not accept.



ame_____ Hosp.No._____ Study No._____ Date of Admn_____

ral Fluid A B (circle one)

LAB FLOW SHEET

| lood | Time Date | Admn | 4HR | 8HR | 16HR | 1 Day | 2 Day | 3 Day | 4 Day | 5Day |
|---|---|---|---|---|---|---|---|---|---|---|
| ct | | | | | | | | | | |
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| K | | | | | | | | | | |
| Osmolality | | | | | | | | | | |
| Sp. Gravity | | | | | | | | | | |
| Stool | | | | | | | | | | |
| ME:rbc/hpf | | | | | | | | | | |
| Leukecyt | | | | | | | | | | |
| OEP* | | | | | | | | | | |
| P | | | | | | | | | | |

Gluc
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hydroly

## SECTION III

1. Personnel Services

| Name | Position | % of Effort | Annual Salary | Taka | Dollars |
|---|---|---|---|---|---|
| Dr. David Sack | Principle Investigator | 30% | $ 34,750 | | 10,425 |
| Dr. Shiraz | CO-Investigator | 20% | Tk.36,384 | 7277 | |
| Dr. Rabbani | " | 20% | Tk.27,084 | 5417 | |
| Dr. Asma | " | 20% | Tk.27,084 | 5417 | |
| Dr. Brown | " | 10% | Tk.20,000 | 2000 | |
| Additiona Study Physician | " | 20% | Tk.27,084 | 5417 | |
| Epidemiology Technician | | 25% | Tk.20,484 | 5121 | |
| 3 study nurses | Study Nurse | 25% | Tk.16,284 | 12213 | |
| Akbar Ali | Study Technologist | 10% | Tk.32,076 | 3208 | |
| Key Punch Clerk | 5 days @ Tk.32/day | | | 160 | |
| Mr. Rahman | Biochemistry Technician | 40% | Tk.27,084 | 10834 | |
| | | | Sub Total: | 57064 | 10,425 |

2. Supplies

| | Unit Cost | Amount required | | |
|---|---|---|---|---|
| Office Supplies,misc. | | | 1,000 | |
| IBM Cards | $ 8 | 10,000 cards | | |
| Computer tapes | $ 8.19 | 2 | | 8.00 |
| Plastics,glassware | | | | 16.00 |
| Infant mice | Tk.3/- | 5400 | 16,000 | 1,000.00 |
| Tb syringes | $ 0.26 | 1800 | | 4.28 |
| BHI media | 0.16 | 1800 | 288 | |
| 1½ ml vials, polypropylene | | 1800 | | 100.00 |
| Nutrient agar, 1 lb | $ 10.00 | 1 | | 10.00 |
| Clinitest tablets, bottles of 100 | | | | 420.00 |
| Computer time | | | | |

3. Equipmer

4. Hosp

5. 12

Attachment to Budget # 1

ROUTINE TESTS

| Biochemistry Lab | # tests required | Cost/test(Tk) | Cost Total |
|---|---|---|---|
| Serum $Na^+$ | 1500 | 0.5 | 750 |
| $K^+$ | 1500 | 0.5 | 750 |
| $Cl^-$ | 1500 | 0.25 | 375 |
| $CO_2$ | 1500 | 1.0 | 1500 |
| Glucose | 1500 | 1.0 | 1500 |
| Creatinine | 300 | 1.0 | 300 |
| Urine $Na^+$ | 600 | 0.5 | 300 |
| $K^+$ | 600 | 0.5 | 300 |
| Osmolality | 600 | 1.0 | 600 |
| Stool $Na^+$ | 300 | 0.5 | 150 |
| $K^+$ | 300 | 0.5 | 150 |
| | | Total Biochem | Tk.6675 |

Clinical Pathology

| | | | |
|---|---|---|---|
| Blood CBC | 300 | 5.5 | 1650 |
| Hct | 1200 | 2.0 | 2400 |
| Urine urinalysis | 300 | 4.0 | 1200 |
| Sp. Gravity | 1500 | 0.25 | 375 |
| Stool Micro exam | 300 | 2.00 | 600 |
| Dark field | 300 | 1.0 | 300 |
| | Total Clin. Path. | Tk. | 6525 |

Bacteriology

| | | | |
|---|---|---|---|
| Culture of stool | 300 | 15.50 | 4650 |
| | Total of Routine tests | Tk. | 17,850 |

## B. BUDGET SUMMARY

| | Category | Year 1 Taka | Year 1 Dollars | Year 2 Taka | Year 2 Dollars | Year 3 Taka | Year 3 Dollars |
|---|---|---|---|---|---|---|---|
| 1. | Personnel | 57,064 | 10,425 | None | | None | |
| 2. | Supplies | 20,088 | 1,982 | | | | |
| 3. | Equipment | - | - | | | | |
| 4. | Hospitalization | 179,850 | - | | | | |
| 5. | Outpatients | 15,000 | - | | | | |
| 6. | CRL Transport | 890 | - | | | | |
| 7. | Travel Persons | - | - | | | | |
| 8. | Transportation Things | - | - | | | | |
| 9. | Rent/Communication | - | - | | | | |
| 10. | Printing/Reproduction | - | - | | | | |
| 11. | Contractual Service | 6,000 | - | | | | |
| 12. | Construction | - | - | | | | |
| | Total: | 279,592 | 12,707 | | | | |

Total $ 31,346

Conversion Rate $ 1.00 = Tk. 15/-

## REFERENCES


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Mahalanabis, D., et. al. The use of Ringer's lactate in the treatment of children with cholera and acute non-cholera diarrhoea. Bull. Wld. Hlth. Org. 46: 311-319, 1972.

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Nalin, D.R., et. al. Oral (or nasogastric) maintenance therapy for cholera patients in all age-groups. Bull. Wld. Hlth. Org. 43: 361-363, 1970.

Palmer, D.L., et. al. Comparison of sucrose and glucose in oral electrolyte therapy of cholera and other severe diarrheas. In preparation.

Sack, R.B., et. al. The use of oral replacement solutions in the treatment of cholera and other severe diarrhoeal disorders. Bull. Wld. Hlth. Org. 43: 351-360, 1970.

World Health Organization. Management of cholera and other acute diarrhoeas in adults and children. WHO/BD/Cholera/74.27.

Bart, K.J., et. al. Single solution for oral therapy of diarrhoea. Lancet 2: 633-634, 1976.

Hirschhorn, N. Single solution for oral therapy of diarrhea - reply (letter). Lancet 2: 634-635, 1976.

Consent Form - Sucrose vs. Glucose Electrolyte Oral Solution in the treatment of Diarrhea of Infants.

The Cholera Research Hospital is carrying out studies to determine the most effective way to treat diarrhea in infants. We would like your child to participate in a study which is attempting to determine the effectiveness of two different sugar-salt solutions, given by mouth, in the treatment of diarrhea in infants. Both of these solutions are effective in adults and older children. This study is being carried out by Drs. Sack, Shiraz, Rabbani and Asma. If you decide to have your child admitted into the study you can expect the following:

1. Your child will be treated for diarrhea.

2. Your child would need to remain in the hospital until he/she has stopped having diarrhea for one day.

3. He (she) will receive as part of his treatment one of two oral sugar-salt solutions, which you will help give. The solution will be marked either "A" or "B".

4. While your child has diarrhea, he will need to have blood tests each day. These are all routine tests and no special or hazardous tests will be done.

5. While diarrhea can be dangerous for an infant, there is no extra risk from participation in this study. If the oral solution is not adequate treatment for your child, we may have to give intravenous solution.

6. You do not have to include your child in the study. If you decide against admitting him (her) to the study, he (she) will be treated at CRL for his (her) diarrhea.

7. You may ask questions about the study at any time.

8. You may withdraw your child from the study at any time, without jeopardizing his (her) medical care.

9. The medical records of your child will be kept confidential.

10. We would like your child to return for a blood test 10 days after he/she is discharged. You will be paid Tk. 15/- plus transportation costs to return for this test.

If you agree to allow your child to participate in this study, please sign your name here.

_____

Date _____

_____Investigators signature.

Review Board on the Use of Human Volunteers

ABSTRACT SUMMARY

Sucrose vs Glucose Electrolyte Oral Solution
in the Treatment of Diarrhea in Infants

1. Approximately 300 children, aged 3 months to 4 years, of greater than 4 Kg. with uncomplicated watery diarrhea will be admitted into the study. Children must be used in this study because this is the only age group infected with rota-virus which is a major cause of diarrhea in infants. Also infants are the major target group for oral hydration therapy.

2. Risks of this study are very small. While dehydration and electrolyte imbalance are possible complications resulting from diarrhea, patients will be closely followed, 24 hours per day, by physicians to avoid these complications. Venapuncture blood samples will be required daily; this is a discomfort but not a significant risk.

3. Physicians will be present 24 hours daily during the study to detect any treatment failures at an early stage and take necessary action.

4. Patients will be identified by number. All records will be kept in a locked office. At the end of the study, identifying information will be removed from study data sheets.

5. Signed informed consent will be obtained from the parent(s). The study will be explained to the parent(s) in Bengali and consenting parents will sign (or thumb print) the Form. They will also be given a copy of the consent Form.

6. N.A.

7. The patient will benefit by the treatment of his diarrhea, society, especially of rural or under developed countries, will benefit by determining the efficacy of the oral solutions in the treatment of diarrhea of infants.

8. Data will be collected from the patients hospital record. Blood, stool, urine will be collected from patients for study.

## PROCEDURES FOR MAINTAINING CONFIDENTIALITY

Patients admitted to the study will be given a study number; records will be kept according to study number and all data will be kept in a locked file in the investigator's locked office. Following completion of the study, all identifying information will be cut off from the data sheet and the clinical information only will be kept at the Cholera Research Laboratory in a locked storage office. Results of the study will be published in a medical journal and no identifying information will be included in the report of this study.