CHAPTER II

METHODOLOGY

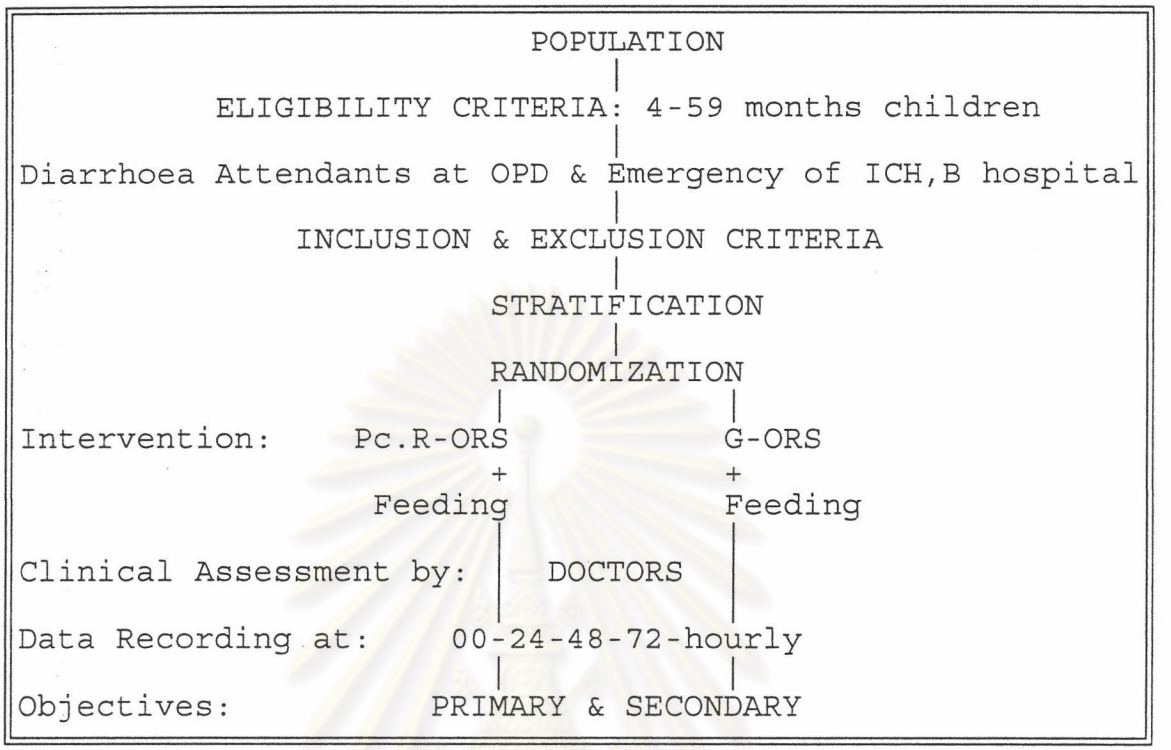
9. RESEARCH DESIGN

Randomized Control Trial:

This is a prospective experimental study which compares the efficacy of Pc.R-ORS and standard G-ORS on acute watery diarrhoea of 4-59 months old children. The group intervened with Pc.R-ORS is the study group and the group with G-ORS is the control group. The trial is unable to use a gold standard ORS as control. Since 1960, any ORT is available with 100% efficacy. The WHO recommended G-ORS is the available standard ORS. Therefore, a better ORS is sought in comparison to G-ORS.

The subjects are included randomly by stratification on age groups at one year interval and on clinical dehydration (no and some). Other confounders are controlled by inclusion and exclusion criteria. Then the subjects are randomly allocated to respective intervention. No study on R-ORS was blinded. And it is not possible to blind subjects, mothers and clinical personnel about the two distinct forms of ORS. The objective outcome variables are recorded from clinical assessment by doctors. Data is collected by the investigator from clinical records.

9.1.1. Figure 2. **Schematic Diagram of Research Design**



Overview of Schematic Diagram of Research Design:

Out of total population, 4-59 months old children are the eligible subjects of this study. As per sample size the subjects are screened through certain inclusion and exclusion criteria from the diarrhoea attendants at OPD and Emergency department of Institute of Child Health, Bangladesh (ICH,B) Dhaka for 3 months. The subjects are assigned through stratified randomization to either the Pc.R-ORS or the G-ORS. The subjects are then given the relevant ORS solution and encouragement of equal early feeding. Four doctors assess the clinical outcomes variables at 4 hourly up to 72 hours. The efficacy of both ORS as primary outcome (recovery by day 3) and secondary outcomes are compared by data analysis.

10. POPULATION AND SAMPLE

10.1. The study is implemented in the diarrhoea research and observation ward of the ICH.B (Institute of Child Health, Bangladesh) hospital, Dhaka. This is a child health research and service delivery hospital having a history of 15 years tradition with a good reputation.

10.2. Total 12 months. (July 1, 1995 to June 30, 1996). The data collection is implemented for 3 months with effect from January 6, 1996.

10.3. Population: About 12m people live in the capital city of Bangladesh, Dhaka which is about 10% of country's total population. The people are from all areas of the country. In Dhaka, about 80% of people live in low socio-economic status as oppose to 85% of the total population. The safe water access in Dhaka[1] is less than over all Bangladesh (83%). The diarrhoea endemicity is comparable with rest of the country. Eligible population are the 4-59 months age group having highest incidence of diarrhoea and case fatality[17].

10.4. Sampling: All the diarrhoea patients of Dhaka city have a free access and equal right to attend the OPD and emergency department of ICH,B hospital Dhaka, irrespective of age, sex, and social status. Patients can attend the OPD and emergency department directly without any referral.

10.5. INCLUSION CRITERIA:

1. Age: 4-59 months - Children aged less than 4 months are not routinely given R-ORS.

2. Sex: Both boys and girls - It is an ethical issue that both boys and girls have equal right to participate in study.

3. Watery diarrhoea - Passing of loose stool. The normal stool is formed stool. Babies on breast feed pass soft stool. Therefore, mothers reporting on the definition of loose or watery diarrhoea is accepted[2]. For a definite watery diarrhoea, the subject must have at least 3 loose motions in last 24 hours without visible blood and / or tenesmus/cramps.

4. Onset of diarrhoea: 24-96 h - Time of appearance of first loose motion as reported by mother. The minimum onset of time is 24 hours. To study acute diarrhoea without other therapy, the upper extent of onset of diarrhoea is 96 hours. The reporting time is recorded with 2 hours accuracy.

5. ≥3 stool in last 24 hours - A reporting of ≥3 stool in last 24 hours is screened for inclusion.

6. Dehydration status: None and some - Following the WHO guide lines[2], dehydration is assessed by doctor (Table 8).

10.5.1. **TABLE 8. ASSESSMENT OF DIARRHOEA SUBJECTS FOR DEHYDRATION STATUS**

PROCEDURES	SIGNS		
LOOK: Condition	Well, alert	*Restless, Irritable	*Lethargic, Unconscious
Eyes	Normal	Sunken	Very Sunken
Tear	Present	Absent	Absent
Mouth & Tongue	Moist	Dry	Very dry
Thirst	Drinks normally not thirsty	*Drinks eagerly hirsty	*Drinks poorly unable to drink
FEEL: Skin pinch on abdomen	Goes back quickly	*Goes back slowly	*Goes back very slowly
DECIDE:	No signs of dehydration	≥2 sign with 1 * sign	≥2 sign with 1 * sign
DEHYDRATION:	**NONE**	**SOME**	**SEVERE**

7. Nutritional status: >79% of weight/height of NCHS (National Center for Health Statistics) median: The children having less than 70% of Wt/Ht are graded as malnourished and are not fit for study.

8. Afebrile: The normal temperature is 98 to 98.6°F.. Due to diurnal variation 99°F is considered as afebrile. Axillary temperature is recorded for one minute.

9. Informed consent - There is no risk and no invasion of true privacy is contemplated, still a signed consent in Bengali is obtained from subject's parent. The purpose of the proposed study and possible outcome for diarrhoea patient are explained to the parents (Form 4, page 78).

10.6. EXCLUSION CRITERIA:

1. Cholera - Cholera cases are identified through dark field microscopy and are excluded. Since, cholera cases need antibiotics and this is a co-intervention for this study.

2. Blood in stool is dysentery and needs antibiotics.

3. Abdominal cramp or tenesmus - Usually reported by mothers as frequent crying of baby or straining during motion. These are the cardinal points of dysentery.

4. Other infection or disease may need antibiotics or drugs. The antibiotics, antisecretory drugs and opiates have some impact on the gut and may interfere the efficacy of ORT.

5. Any therapy for diarrhoea - Use of G-ORS and antibiotic or other antidiarrheal drug may have impact on the gut which may interfere with the efficacy of ORT, especially the use G-ORS. Because. the control group is given G-ORS.

6. Persistently vomiting and severely dehydrated : As per the WHO guide lines these cases are treated with IV fluid for initial rehydration.

7. Mentally retarded child or mother are excluded for ethical reason. child with sick or pregnant mother.

10.7. SAMPLE SIZE[87]:

Primary Outcome - Recovery rate by day 3 (72 h)[16,35]

Recovery rate on Pc.R-ORS: P_1

Recovery rate on G-ORS: P_2

Null Hypothesis : $P_1 - P_2 = 0$

Alternative Hypothesis : $P_1 > P_2$ or $P_1 < P_2$

It has been found that >95% of patients with watery diarrhoea on R-ORS with feeding recover by day 3 in ICDDR,B hospital[86]. A 22.5% difference is expected to be clinically significant. Since, >95% of patients with watery diarrhoea on R-ORS with feeding recover by day 3 in ICDDR,B hospitals, for Pc.R-ORS with feeding at least a 92.5% recovery may be expected in the same period.

Therefore, with recovery rates of : 92.5% and 70%

Level of significance : 5%

Power of the test :80%

$N = [(Z\alpha/ P_1(1-P_1) + Z\beta/ P_2(1-P_2)) / (P_1-P_2)]^2$

N = 55 for each group (EPIINFO)

Expected Drop-out (R)[88] = 8% (previous observation)

$N_d = N / (1-R)^2$ = 63.1 or 64 subjects for each group

10.8. Procedure of Stratified Randomization:

a. Data collection period 3 months = 90 days
b. 6 admission days per week = 70 admission days
c. 2 subjects per admission day X 70 admission days = 140 subjects
d. Total sample size = 128 subjects

e. 128 subjects are stratified into 10 strata by one year interval and dehydration status (none and some).

g. Following the informed consent, the first subject is asked by the assigned doctor to take a half of code card and other half is given to second subject in the same stratum. The subjects are sent to the study ward. The concerned attending nurse assigns ORT intervention according to code.

i. There are 12-13 subjects per stratum. When all cases are found in any stratum, the next available case fitted with this stratum are included. By this way the proportionate number of diarrhoea subjects per stratum are included.

11. MANEUVER :Observation and Measurement

11.1. OBSERVERS: The study assigned 4 doctors and 4 nurses. 3 doctors and 3 nurses are required per 24 hours. Another 1 doctor and 1 nurse are required to compensate leave coverage and to be remained stand by.

11.1.1. On Admission (00 h): Doctors examine the subject and note baseline data on the clinical record form.

11.1.2. During Hospital Stay: The Doctors assess the patients and record the clinical outcomes on clinical record form at 4 hourly and on call according to a check list of activities. They also maintain the balance sheet (FORM. 1) input (ORS and food) and output (stool, urine and vomitus). They prescribe investigation and therapy according to the patient's condition and the treatment category for the study. Attending nurses carry out the instructions.

11.1.2. FORM 1. BALANCE SHEET FOR INPUT & OUTPUT

ID# |_|_|_|

INPUT IN ml					
YY-MM-DD	hh	ORS	YY MM DD	hh	FOOD

OUTPUT IN ml								
YY-MM-DD	hh	STOOL	YY-MM-DD	hh	URINE	YY-MM-DD	hh	URINE

11.2. MEASUREMENT

The variables are recorded 24 hourly from the time of admission at 00 h to 72 h (day 3).

(24 hours: or One day is the unit of time from the time of admission (00 h or 0 day) to end result during hospital stay or retrospectively to the onset of diarrhoea).

11.2.1. VARIABLES MEASURED AT BASELINE (00 h):

1. Identification number - 1 to 128 total sample subjects.

2. Age - The minimum age of a subject is 4 month. The 16th day should be the minimum cutoff point for rounding a month. Based on the local calendar and social events the mother's reporting is the primary source of the age of the infant. Mothers can recall the age with in one month accuracy. No variable is expressed in relation to age. Therefore, the use of rounded age will have no influence on any outcome.

3. Date of onset of diarrhoea - The mother can give an exact date of onset of diarrhoea to within a maximum of 4 days recall. The date is recorded as year, month and day.

4. Time of onset of diarrhoea - Mentioned in inclusion.

5. Date of admission - Exactly.

6. Time of admission - It is recorded exactly with rounding the hour at 30 minutes cutoff point.

7. Frequency of stool - Number of loose motions in last 24 h. This is a baseline variable. It is obtained from today's current time to yesterday's same time. It is recorded as interval data and exactly.

8. Weight in gram - The child is weighed without cloth, using a weighing machine with 10 g precision. This variable is used to determine the Wt/Ht% of median NCHS and weight change.

9. Height in mm - The height is measured with a length scale in supine position from vertex to heel with 1 mm accuracy.

10. Dehydration status are None, Some, and severe as per the WHO guideline[2] (Table 8). The doctors are careful to examine the tongue by touching it with a dry and clean finger. (But not just after vomiting and a drink).

11. Temperature - Mentioned else where.

12. Pulse rate - The femoral pulse is recorded for one minute. Higher than normal pulse rate with low volume or feeble pulse indicates dehydration and hypovolemic state.

13. Respiration is counted during a quite period for one minute. A rapid respiration indicates metabolic acidosis.

14. Blood pressure in mm Hg is recorded with a small cuff and a digital sphygmomanometer. A low blood pressure indicates dehydration and a hypovolemic state. The study follows the Table 9. for pulse, respiration and blood pressure[89]:

11.2.1. **TABLE 9. NORMAL RANGE OF PULSE, RESPIRATION AND BLOOD PRESSURE IN CHILDREN**

GROUPS	PULSE Rate/minute	RESPIRATION Rate/minute	BLOOD PRESSURE mm Hg Systolic / Diastolic	
Infants	:120 - 150	30 - 60	87 - 105	53 - 66
Toddlers	:90 - 130	20 - 40	95 - 105	53 - 66
Preschool	:80 - 110	22 - 34	95 - 105	53 - 66

15. Stool sample is collected from the first motion for microscopy to exclude cholera and bloody diarrhoea.

16. Intervention - The nurses prepare the Pc.R-ORS or G-ORS (Table 6) and instruct the mothers to feed with cup and spoon as much as child can take or frequently according to the WHO guide line (Table 10).

11.2.3. VARIABLES MEASURED AT 24 HOURLY:

1. Date of record and time of record

2. Frequency of stool - The subject is put in diarrhoea cot and is always provided with 4 tagged pre weighted towels. The 1st one is for stool collection, the 2nd one is for urine, the 3rd one is for vomitus and the 4th one as reserve. Number of motion is recorded by pre weighted towel count. A new towel is replaced to collect the next motion and so on. A 24 hours frequency of motion is recorded by doctors.

3. Stool consistency is recorded from each motion as watery or formed and is plotted on form 1. with the date and time of motion with 1 h accuracy. From this plotting, the point of recovery is estimated. To confirm a formed stool, the subject is observed for the next 24 hours from the time of appearance of a formed stool.

5. Amount of stool output is recorded in g / motion with 1 gram accuracy by immediate weighing of the used pre weighted towel. Then stool output is expressed in ml /kg /24 h. Nursing attendants are remain careful to collect stool and urine separately. Mothers are also instructed to cooperate with the nursing attendants.

FORM 2. **DETERMINATION OF DIARRHOEA RECOVERY & TIME OF RECOVERY BY PLOTTING STOOL CONSISTENCY AND STOOL FREQUENCY**

(Yes=Y No=N)

DATE YY-MM-DD	TIME h	CONSISTENCY OF STOOL Loose	Form	No	
					Last motion before admission
					Motions after admission
					Up to a maximum of 96 h

6. The output of urine is recorded by the pre weighted towel and is expressed in ml /kg /24 h.

7. The output of vomitus is collected by separate pre weighted towel and estimated by weighing with 1 g precision. Any spill over amount is also recovered and expressed in ml /kg /24 h.

8. Weight in gram - (10 g precision)

9. Dehydration status - None, some and severe

10. Pulse - Rate /m

11. Temperature - <99°F

12. Respiration - Rate /m

13. Blood pressure - mm Hg (Digital)

14. ORT intake - The amount of ORT consumed by a child is recorded from the remains of ORT in the ORT jug. The measurement of ORT is done by nurses in 1 ml accuracy. Then the amount is converted to ml /kg /24 h.

15. Onset of food intake - All the children are provided with food according to their age group. The onset of food intake is recorded in h between onset of ORT and onset of food intake. For breast feeds, mothers put the baby on her breast and babies suck milk as normal for some time. For other children, they take food eagerly or ask for food.

16. Amount of food intake - All the children are provided with food according to their age group i.e. 6 meals /24 h for the children over 18 months and 8 meals /24 h for rest except those who are exclusively breast feed[2]. The amount consumed is estimated by deducting left over food from pre-weighed food with 1 g precision. The mothers are instructed to weight themselves just before and after breast feeding to estimate the amount of milk fed (food is expressed in ml /kg /24 h).

17. Serum electrolytes - Sodium, potassium. bicarbonate, and urea are assessed for the poorly hydrated patients. If needed such patients are withdrawn from the study as failure of ORT. They are then given standard treatment for dehydration.

18. End result: Recover, Failure of ORT and Drop-out

11.3. INTERVENTION

Study : Precooked Rice-ORS

Control: Standard Glucose-ORS

On admission the nurses prepare respective ORT (Table 5, page 8) and instruct the patient's mother to feed ORT according to the following regimen (Table 10) for the correction of dehydration at the initial rehydration phase of 4 hours[2].

11.3.1 TABLE 10. **WHO GUIDE LINES FOR REHYDRATION ACCORDING TO BODY WEIGHT AND DEHYDRATION STATUS**

Wt in kg	**<5**	**5-7.9**	**6-10.9**	**11-15.9**	**16-29.9**
Some dehydration: **ORT in ml**	**200-400**	**400-600**	**600-800**	**800-1200**	**1200-2000**
No dehydration: **ORT in ml**	**100-200**	**200-300**	**300-400**	**400-600**	**600-1000**

For the maintenance phase of rehydration, the feeding of ORT amount is equal to the volume of stool output and vomitus. Mothers are encouraged to feed their children by cup and spoon with frequent small feedings. They are instructed to feed ORT until diarrhoea stops.

FEEDING: Feeding of food and home fluids are equally encouraged in both groups.

FOOD: Recommended dietary menu, routinely followed at ICH,B hospital. Home fluids and solid food are altogether defined as food and are provided by hospital.

COMPLIANCE: The compliance of ORT is defined as the amount of ORS solution consumption by the patients with diarrhoea according to the guidelines of ORT regimens for initial and maintenance phases of rehydration.

NON-COMPLIANCE: Patients who refuse to take ORT or are unable to follow the regimens of rehydration will be classified as non-compliant.

CO-INTERVENTION: The possible co-interventions are antibiotics, antisecretory, and antispasmodic drugs. The diarrhoea patients with cholera, dysentery and other infections are carefully excluded from study during admission and treatment period. So the use of antibiotic is not necessary. Other antisecretory and antispasmodic drugs are not recommended to use for acute watery diarrhoea.

12. DATA COLLECTION

12.1. Extrinsic Quality Control: Routine and spot supervision and monitoring of clinical activities by the Chief physician.

12.2 Intrinsic Quality Control:

12.2.1 Two times pretesting of data form before study

12.2.2. Reliability Tests: are done at ICH,B Hospital, Dhaka for 3 weeks (January 6-28, 1996).

RATERS, NATURE OF VARIABLES, THEIR IMPORTANCE & STATISTIC:
For Inter-rater Reliability Testing of Multiple Comparison:

NATURE OF VARIABLES/DATA		IMPORTANCE	STATISTIC
RATERS: 4 DOCTORS			
Stool consistency:	Dichotomous Subjective	To define primary outcome. Secondary outcome.	ICC
Stool frequency	:Interval Objective Hard	To define primary outcome. To assess prognosis. Secondary outcome.	ICC
Dehydration	:Ordinal Subjective	Vital sign of prognosis. Secondary outcome.	ICC
Stool output	:Ratio Objective	To assess prognosis. Secondary outcome.	ICC
RATERS: 4 NURSES			
ORS solution	:Ratio Objective	To assess compliance. Secondary outcome.	ICC

ASSUMPTIONS: Subjects are independent. Raters are assigned to the study randomly and measure variables independently.

SUBJECTS & METHODS: Sixteen U-5s children with acute watery diarrhoea are admitted through screening criteria. Eight subjects are randomly allocated to Pc.R-ORS another eight to G-ORS. They are treated and observed as per methodology.

REPETITIONS OF OBSERVATION: For the reliability testing each subject is assessed for 4-5 minutes by each doctor and 1-2 minutes by nurses to measure the relevant variables. These observations are conducted once in any day of hospital stay of the patient. So, 6 subjects on 1st week, 5 on 2nd week and another 5 on 3rd week are randomly observed.

STATISTIC: Intra-class Correlation Coefficient (ICC, r_1) is a reliability coefficient that is expressed by using variance estimates obtained through an analysis of variance. For single rating score of multiple comparisons of inter-rater reliability test, the formula of ICC is

r_1 = BMS-EMS / BMS + (k-1)EMS + k(RMS-EMS)/n,

where BMS is between-subjects mean square, EMS is error mean square, RMS is between-rater mean square, k is number of raters and n is number of subjects. It reflects both degree of correspondence and agreements. Statistically it has some advantages. First, it can be used to assess reliability among more than two raters. Second, it is designed for use with interval data like stool frequency and ratio data like stool output and ORS solution intake. Dehydration status is a ordinal data with 3 outcomes and k_w is applicable only for pair raters comparison. But for multiple comparison the ICC can be applied without distortion to data on the ordinal scale when intervals between such measurements are assumed to be equivalent. So, the ICC is applicable for dehydration status as it is measured with 3 ratings: None (<5% wt. loss), Some

(5-10%) & Severe (>10%). The data that are rated as a dichotomy, the ICC has been shown to be equivalent to measure of nominal agreement, simplifying computation in instances where more than two raters are involved[90]. In this study, the stool consistency is a dichotomous data (formed and watery) and four doctors are involved. Moreover, stool frequency and stool consistency are jointly used to define primary outcome (recovery). Since, ICC is applicable for stool frequency, same index should be used for stool consistency. Therefore, the ICC statistic is logically applicable for multiple comparisons on stool consistency. The ICC 1 is a perfect and desired reliability but in practice it is very hard to achieve such target. For most clinical measurements, the ICC >.90 ensure a reasonable reliability[90].

RESULT: **Inter-rater Reliability Testing (Multiple Comparisons)**:

Stool consistency: r_1 = 0.941,

Dehydration: r_1 = 0.918

Stool frequency: r_1 = 1.00

Stool output: r_1 = 0.998

ORS solution: r_1 = 0.959

12.2.3. Validation of weighing scale, Pre weighted tagged towel, ORT jug and cup are done before study and once a week during study with the respective standard scale.

12.2.4 Provision of written detailed instructions

Check-list of activities for the doctors, clinical clerk and nurses are prepared to follow the procedures of study.

12.2.5. Data Checking, Verification and Computer Entry:
Data checking and verification is done with clinical records. The data form is designed in pre-coded with detail layout (FORM 3, page 112) to minimize the transfer error. It is pretested twice before the data collection. The investigator collect data from clinical records on admission and then 24 hourly up to 72 h. Then he concurrently entered data by using Dbase package.

12.5 **DETERMINATION OF VARIABLES FOR ANALYSIS:**

12.5.1. Comparison groups: Pc.R-ORS and G-ORS

12.5.2. Base Line variables on admission:

VARIABLES	DATA TYPE
Age of children in months	: Interval
Onset of diarrhoea in hour	: Interval
Frequency of stool in last 24 hours	: Interval
Dehydration status: None and some	: Ordinal
Nutritional status: wt/ht% of median	: Interval

12.5.3. DETERMINATION OF OBJECTIVE OUTCOME VARIABLES :
1. End result of treatment are recover from diarrhoea, failure of ORT and drop-out. There is no drop-out category. Therefore, the primary outcomes are recovery and failure.

2. Recovery from diarrhoea is determined from three variables: frequency of stool, consistency of stool and time of recover.

3. Duration of Diarrhoea on ORT is determined in hours from the time of admission and time of recovery. The total duration of diarrhoea is computed by adding the duration of diarrhoea before admission to the duration of diarrhoea whilst on ORT.

4. SECONDARY OUTCOMES: Subjects recovered on ORT within 3 days or followed-up are included for analysis of secondary outcomes. In the list below /24 h interval means observations variables on days 1, 2 and day 3 (Table 11).

12.5.3. TABLE 11. **OUTCOME VARIABLES AND DATA TYPE**

OUTCOME VARIABLES	DATA TYPE
End Result:Primary outcome & drop-out :	Nominal
Primary outcome: Recover and failure :	Nominal
Duration of diarrhoea: between onset of ORT and recover in h :	Interval
Total duration of diarrhoea: between onset of diarrhoea & recover in h :	Interval
ORT intake in ml/kg /24 h :	Ratio
Onset of food intake after ORT (minute) :	Interval
Food intake in g/kg /24 h :	Ratio
Stool output in ml/kg /24 h :	Ratio
Stool frequency: number/24 h :	Interval
Stool consistency: watery & formed /24 h:	Nominal
Urine output in ml/kg /24 h :	Ratio
Vomitus in ml/kg /24 h :	Ratio
Dehydration status: no & some /24 h :	Ordinal
Weight change in g/kg /24 h :	Ratio

13. DATA ANALYSIS

13.1 Soft Ware: Dbase / SPSS PC+ /EPIINFO /Xedit / HG

13.2 Hard Ware: PC AT 80

Step I: Transfer of Dbase data to SPSS system data.

Step II: Frequency tables of objective outcome data by intervention are constructed to see the type of distribution.

Step III: Tabulation of nominal and ordinal data by intervention and Mean±SD (SD:mean of standard deviation) of interval and ratio data by intervention are done.

Step IV: The statistical testing are done with 95% confidence limit and significance is expressed as P:≤.05. The Chi-square test for 2X2 tables is used to determine the association of dehydration status and sex of study subjects at baseline and recovery of diarrhoea with intervention. Chi-square test of trend is used to determine the association of age groups and nutritional status at baseline. Two tailed independent t-test is used for age, stool frequency at baseline and duration of diarrhoea. 2X2 table is used to describe the dehydration status and stool consistency during the 3 observation days. Mean±SD are used to describe the data on frequency of stool, stool amount, vomitus, urine, ORS solution, food intake, onset of food intake, duration of diarrhoea, and weight change during the 3 observation days. If mean is less than SD, then logarithmic transformation is done.

14. ETHICAL REVIEW

14.1. The study is obliged to follow all ethical aspects imposed by Ethical Review Committee (ERC) of ICH,B.

14.2. Since Pc.R-ORS is a newer product, it is tested first for efficacy. Because U-5s are the critical sufferers of diarrhoea, it is used on U-5s. Boy and girl are equal suffer of diarrhoea, so it is tested on both. To ensure the safety of children any untoward symptom or side effect is to be reported promptly for necessary action or withdrawal from intervention for necessary treatment. The study follows the CDD recommended method to manage diarrhoea patients. Doctors monitor, evaluate and prescribe therapy at 4 hourly and on call. Nurses provide services according to doctors' instructions. So, there is no risk.

14.3. The confidentiality of data collected is maintained and information are not passed to any one. Anonymity of the subjects are assured through the use of code numbers. There is no risk or invasion of privacy is contemplated, still a signed consent in Bengali is obtained (FORM 4. in English). The purpose of the proposed study and the potential outcomes for a diarrhoea patient is explained to the concerned attendant or the mother.

14.4. The result of the study will help to introduce a cheaper, readily available, and more effective ORT by using nation's own resources. Consequently people will get confidence to make homemade Rice-Salt Solution. If necessary to monitor the patient's status, the study may collect 5 ml blood. This would not cause any harmful effect.

14.3.1. FORM 4. CONSENT FORM (used in Bengali)

This is to inform you that the Chemical Dept. of BUET has developed a precooked Rice-ORS which does not need cooking and readily suspends/dissolves in water. It needs clinical testing on acute watery diarrhoea of under-5 children.

As a part of Master's thesis of Health Development Program under Thai CERTC Consortium, Chulalongkorn University, Bangkok, Thailand, this Pc.R-ORS is going to be compared with standard Glucose-ORS. It is found that R-ORS is more beneficial than G-ORS. A few numbers of hospitals are using R-ORS which needs cooking.

Your child is admitted for diarrhoea treatment. We would like to allow your child to participate in this study if he fits the screening criteria. Your child will be either treated by Pc.R-ORS or G-ORS according to random chance. In addition, your child will be encouraged to take normal food for diarrhoea as early as possible. The study will last for 4 days or less.

As per study policy, a stool sample will be collected on admission. If needed a sample of 4 ml of blood may be collected to assess the child's condition. Your child will be allowed to go home after 24 hours of recovery from diarrhoea or other necessary treatment are completed. You may choose not to participate in the study. In any case, appropriate treatment of diarrhoea as available in this hospital will be provided to tour child. You can withdraw your child from the study at any time of treatment.

DATE _____ LEI/Signature of Guardian _____ Signature of PI. _____

15. LIMITATIONS AND OBSTACLES

1. The study is not blinded and it is not possible to blind the observers.

2. According to research policy, the study was put in a queue with concurrent other studies on a priority basis.

3. Delay in getting fund for the study.

4. Political crisis and civil unrest

16. EXPECTED BENEFIT AND APPLICATION

1. Rice-ORS will give self sufficiency by averting dependency on external supply of G-ORS.

2. The target people would get free access to Pc.R-ORS with more benefit.

3. Burden of disease could be significantly reduced due to early recovery from diarrhoea

4. Pc.R-ORS would encourage the target users to promote home management of diarrhoea using home ingredients to prepare RSS independently.

5. If practicable, the study would have a profound implication in the primary health care strategy of early management of diarrhoea at home for the control of diarrhoeal diseases (CDD) program of WHO.

17. RESULT

17.1. BASELINE, INTERVENTION AND COMPLIANCE

17.1.1. TABLE 12. Baseline Parameters of the Study Children:

It shows the equivalency for confounding factors. The male children are slightly more than the female in both groups. But male and female ratio are similar for both groups. The range of age are 4-42 months. The mean age of children are slightly more in Pc.R-ORS group than the G-ORS group but not statistically significant. Also the trend of age group distribution are almost similar. Nutritional status as Wt/Ht% of median of NCHS are expressed in both mean and trend. Both the figures are not statistically significant. The range of stool frequency in 24 hours before admission is 3 to 9 in both groups. The average stool frequency is slightly more for Pc.R-ORS group (5.12 ± 1.51) but not significantly differ from G-ORS group (4.92 ± 1.57). The diarrhoea period in hours from onset to admission is slightly more in Pc.R-ORS group than G-ORS group. But the diarrhoea period in hours (h) from last motion to admission is slightly more in G-ORS group than Pc.R-ORS group. Both the differences are not statistically significant. Almost 70% of cases are admitted with no dehydration in either group and the rest are with some dehydration.

TABLE 12. BASELINE PARAMETERS OF THE STUDY CHILDREN

PARAMETERS	Pc.RICE-ORS N = 64	GLUCOSE-ORS N = 64	P
SEX:			
Male	34 (53.12)	34 (53.12)	NS
Female	30 (46.88)	30 (46.88)	
AGE IN MONTHS:			
Mean	17.58	18.64	NS
±SD	8.41	8.58	
Age Groups:			
4-11	16 (25.63)	15 (23.41)	NS
12-23	35 (54.70)	33 (51.62)	
24-35	11 (17.23)	13 (20.25)	
36-59	2 (3.12)	3 (4.72)	
WEIGHT PER HEIGHT OF PERCENT OF MEDIAN OF NCHS:			
Mean	85.97	87.89	NS
±SD	4.86	4.95	
Groups:			
75-80	11 (17.21)	12 (18.42)	NS
81-85	15 (23.42)	14 (21.91)	
86-90	27 (42.26)	27((42.26)	
Mean weight in g	11.73	11.15	NS
±SD	3.73	3.10	
STOOL FREQUENCY IN 24 HOURS BEFORE ADMISSION:			
Mean	5.12	4.92	NS
±SD	1.51	1.57	
DIARRHOEA PERIOD IN HOURS FROM ONSET TO ADMISSION:			
Mean	43.28	42.61	NS
±SD	14.24	13.38	
DIARRHOEA PERIOD IN HOURS FROM LAST MOTION TO ADMISSION:			
Mean	2.96	3.11	NS
±SD	1.18	1.40	
DEHYDRATION STATUS ACCORDING TO W.H.O GUIDE LINES:			
No	45 (70.31)	46 (71.88)	NS
Some	19 (29.69)	18 (28.12)	

P: Probability
() Number in parentheses indicates percentage
NS: No statistical difference

17.1.2. Compliance with ORS Solution According to W.H.O. Guide lines of the Cases Entered into the Study: Following admission into the study the cases are fed respective ORS solution as per the WHO (World Health Organization) guidelines. Out of 64 cases in either group 62 cases comply with Pc.R-ORS solution in R-ORS group and 61 cases comply with G-ORS solution in G-ORS group. The non-compliance cases used less amount of ORS solution in comparison to WHO guidelines.

17.2. IMPACT ON PRIMARY OUTCOMES:

17.2.1. TABLE 13. Outcomes of Cases Treated with ORS Solution as Intervention and Followed-up for 3 Days: By day 3, significantly (P: .005) more diarrhoea cases are recovered in Pc.R-ORS group (82.8%) than those of G-ORS group (60.9%). There by, the failure rate is less for Pc.R-ORS group (17.2%) than G-ORS group (39.1%). Testing the Alternative Hypothesis of Proportion of Recovery by Day 3 for Pc.R-ORS and G-ORS:

$$\frac{\text{Difference of Proportion of Recover}}{\text{Standard Error of Difference of Proportion of Recovery}}$$

(Recovery rate for Pc.R-ORS: P_1 & Recovery rate for G-ORS: P_2, Estimated population recovery rate: p and N_1 or N_2 = 64)

$(P_1 - P_2) \,/\, \sqrt{p(1-p)/N_1 + p(1-p)/N_2} = 2.75$ (Chi-square:7.57)

Since this value is greater than 1.96 $(1-\alpha)$. The difference is not due sampling (chance) variation in two groups. And the sample size is enough to detect the true difference. If this true difference is rejected, there is less than 5% chance of rejecting a true difference of recovery.

Also, difference is observed between two groups for cases continued more than 3 days. Failure of ORT intervention includes the cases of diarrhoea continue more than 3 days and others cases like referred for complication related to ORT, non-cooperation and non-compliance. Statistical significance are not found due to a few number of cases are recorded against these categories.

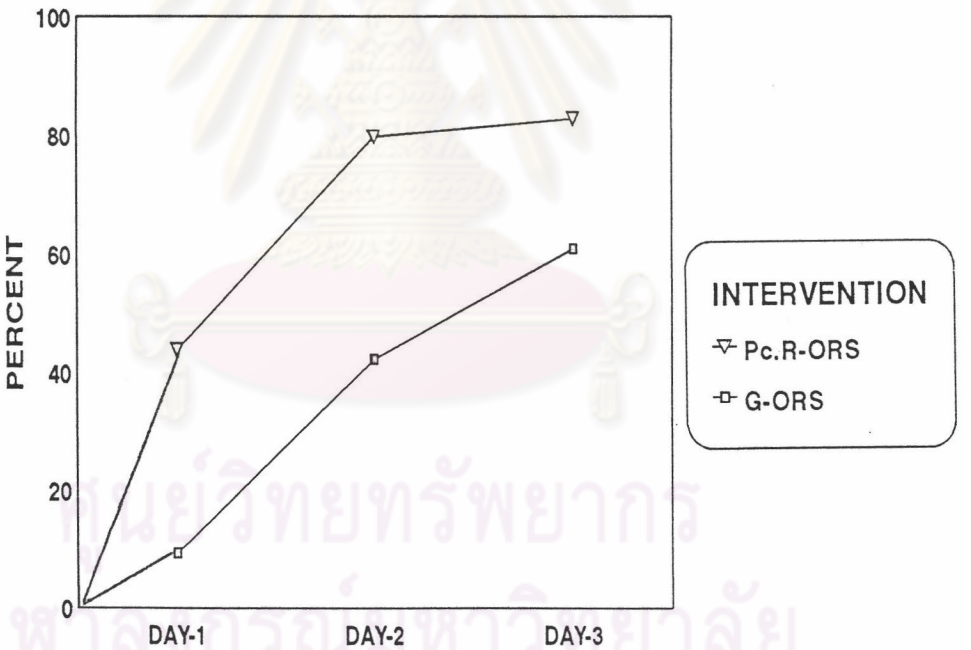
TABLE 13. **OUTCOMES OF CASES TREATED WITH ORS SOLUTION AS INTERVENTION AND FOLLOWED-UP FOR THREE DAYS**

OUTCOMES	Pc.RICE-ORS N = 64	GLUCOSE-ORS N = 64	P
RECOVERED	53 (82.8)	39 (60.9)	.005
FAILED (a+b)	11 (17.2)	25 (39.1)	
a. Diarrhoea continued >3 days	6 (9.4)	18 (28.1)	
b. Others*	5 (7.8)	7 (11.0)	

(): Number in parentheses indicates percentage
* : Complication related to ORT, Non-cooperation/demanded other medication and Non-compliance

17.2.2. FIGURE 3. Cumulative Rate of Recovery of Observed Cases Using ORS Solution: Considering the cumulative rate of recovery by day 1, 43.8% cases have recovered on Pc.R-ORS and 9.4% on G-ORS. By day 2, a greater divergence is seen as 79.7% cases recovered on Pc.R-ORS while only 42.2% of those on G-ORS. By day 3, total 82.8% cases have recovered on Pc.R-ORS and 60.9% on G-ORS.

FIGURE 3. **CUMULATIVE RATE OF RECOVERY OF OBSERVED CASES USING ORS SOLUTION**

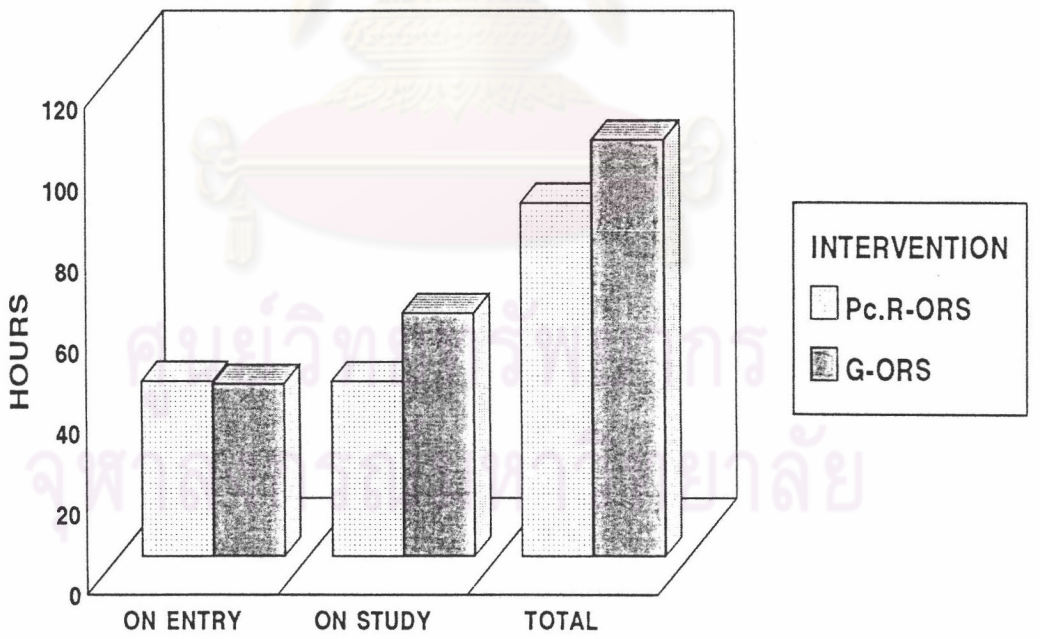


Pc.R-ORS	43.8	79.7	82.8
G-ORS	9.4	42.2	60.9

DAYS OF OBSERVATION

17.2.3. FIGURE 4. Duration of Diarrhoea in Hours for Observed Cases Using ORS Solution: Children of both groups have suffered an equivalent time periods in hour before entering the study. These figures are 43.28 ± 14.24 h for Pc.R-ORS group and 42.61 ± 13.38 h for G-ORS group and are not significantly different. The duration of diarrhoea during intervention period are significantly less (P:.0001) for those on Pc.R-ORS (43.23 ± 26.53 h) than G-ORS (60.06 ± 26.47 h). In terms of total duration of diarrhoea , the Pc.R-ORS group suffered significantly (P:.0001) less period (87.18 ± 31.28 h) than the G-ORS group (102.73 ± 27.83 h).

FIGURE 4. DURATION OF DIARRHOEA IN HOURS FOR OBSERVED CASES USING ORS SOLUTION



Pc.R-ORS	43.28	43.23	87.18
G-ORS	42.61	60.06	102.73

DIARRHOEA PERIODS

17.3. **IMPACT OF INTAKE**

17.3.1. TABLE 14. Status of ORS Solution Intake in ml/kg /24 h During the Observation Days for Cases Using ORS Solution: Mean intake of ORS solution is less for those consuming Pc.R-ORS solution to accomplish prevention of dehydration and recovery than G-ORS on day 1 to day 3 of observation. On day 1, the G-ORS group consume 76.40 ml and Pc.R-ORS group consume 64.80 ml. On day 2, the G-ORS group consume 40.10 ml and Pc.R-ORS group consume 24.82 ml. On day 3, the G-ORS group consume 33.36 ml and Pc.R-ORS group consume 24.30 ml. These figures show a remarkable down trend intake of ORS solution from day 1 to day 3 in both groups.

TABLE 14. **STATUS OF ORS SOLUTION INTAKE (ml/kg/24 h) DURING THE OBSERVATION DAYS FOR CASES USING ORS SOLUTION**

DAYS		Pc.RICE-ORS	GLUCOSE-ORS
DAY-1	N	64	64
	Mean	64.80	76.40
	±SD	19.41	31.50
DAY-2	N	34	55
	Mean	24.82	40.10
	±SD	17.30	22.45
DAY-3	N	10	30
	Mean	24.30	33.36
	±SD	12.36	16.56

17.3.2. TABLE 15. Status of Food Intake in ml /kg /24 h During Observation Days for Cases Using ORS Solution: On entry into the study more amount of food is consumed by Pc.R-ORS group (41.43 ml) than G-ORS group (24.07 ml). On day 2 and day 3, food intakes are not different. But Pc.R-ORS group maintains a stable amount of food intake (more than 40 ml /kg /24 h) than G-ORS group.

On entry into study, the onset of food intake is 2.42 ± 1.54 h for Pc.R-ORS group and 2.72 ± 1.73 h for G-ORS group. This difference is comparable.

TABLE 15. **STATUS OF FOOD INTAKE (ml /kg /24 h) DURING THE OBSERVATION DAYS FOR CASES USING ORS SOLUTION**

DAYS		Pc.RICE-ORS	GLUCOSE-ORS
	N	64	64
DAY-1	Mean	41.43	24.07
	±SD	18.43	10.26
	N	34	53
DAY-2	Mean	41.45	40.86
	±SD	15.23	10.96
	N	10	30
DAY-3	Mean	44.16	34.12
	±SD	16.02	10.75
	ONSET OF FOOD INTAKE IN HOUR		
	N	64	64
DAY-1	Mean	2.42	2.72
	±SD	1.54	1.73

17.4. **IMPACT ON OUTPUTS**

17.4.1. TABLE 16. Status of Stool Output During the Observation Days for Cases Using ORS Solution:

a. STOOL CONSISTENCY: At the point of entry, all the study children's mothers reported a loose or watery stool consistency. By day 1, 37.5% of children on Pc.R-ORS and 15.6% on G-ORS have passed formed stool. By day 2, 70.3% of children on Pc.R-ORS and 42.9% on G-ORS have passed formed stool. By day 3, 40.0% of children on Pc.R-ORS and 41.9% on G-ORS have passed formed stool. The children in Pc.R-ORS group passed more formed stool in day 1 and day 2 than those in G-ORS group.

b. STOOL FREQUENCY /24 h: On entry into the study children's mothers reported an average 5.12 loose motion in last 24 h for Pc.R-ORS group and 4.92 for G-ORS group. These reporting stool frequencies are similar. On day 1, the stool frequencies are higher for G-ORS group (3.58) than Pc.R-ORS group (2.44). Also on day 2 the stool frequencies are higher for G-ORS group (2.62) than Pc.R-ORS group (1.90). On day 3, stool frequencies are similar in both groups .

c. STOOL AMOUNT in ml /kg /24 h: Stool purging rates are further validated from the observation of stool quantity. On day one, 40.02 ml of stool output is noticed for G-ORS group and less amount (28.30 ml) for R-ORS group. And a similar trends are noticed on day 2, day 3.

17.4.2. TABLE 17. Status of Urine Output in ml /kg /24 h During the Observation Days for Cases Using ORS Solution: On day 1, the urine output is 21.83 ml for Pc.R-ORS group and 19.21 ml for G-ORS group. On day 2, G-ORS group has passed higher amount of urine (25.58 .) than Pc.R-ORS group (22.72). On day 3, both the group have passed comparable amount of urine.

TABLE 17. **STATUS OF URINE OUTPUT (ml /kg /24 h) DURING THE OBSERVATION DAYS FOR CASES USING ORS SOLUTION**

DAYS		Pc.RICE-ORS	GLUCOSE-ORS
DAY-1	N	64	64
	Mean	21.83	19.21
	±SD	9.12	11.43
DAY-2	N	34	53
	Mean	22.72	25.58
	±SD	7.24	13.08
DAY-3	N	10	30
	Mean	19.39	19.66
	±SD	8.10	5.74

17.4.3. Status of Vomitus in ml /kg /24 h During the Observation Days for Cases Using ORS Solution: On day 1, 3 children on Pc.R-ORS and 12 children on G-ORS group has passed vomitus. On day 2, one child on Pc.R-ORS and 7 children on G-ORS has passed vomitus. On day 3, both the groups have any vomitus. The data is not enough to estimate any difference.

17.5. IMPACT ON DEHYDRATION AND WEIGHT CHANGE:

17.5.1. TABLE 18. Status of Dehydration During the Observation Days for Cases Using ORS Solution: On admission, about 30% of children have some dehydration in both groups. On day one, 65.6% of children have developed some dehydration in G-ORS group as oppose to 31.2% in Pc.R-ORS group. On day 2 and day 3, most of the cases turn to no dehydration.

TABLE 18. **STATUS OF DEHYDRATION DURING THE OBSERVATION DAYS FOR CASES USING ORS SOLUTION**

DAYS		Pc.RICE-ORS	GLUCOSE-ORS
DAY-0	N	64	64
	No	45 (70.31)	46 (71.88)
	Some	19 (29.69)	18 (28.12)
DAY-1	N	64	64
	No	44 (68.8)	22 (34.4)
	Some	20 (31.2)	42 (65.6)
DAY-2	N	33	52
	No	25 (75.8)	44 (84.6)
	Some	8 (24.2)	8 (15.4)
DAY-3	N	11	31
	No	10 (90.9)	25 (80.6)
	Some	1 (9.1)	6 (19.4)

17.5.2. TABLE 19 Weight Change of the Children During the Observation Days for Cases Using ORS Solution: The data used here are logarithmic transformed from g /kg /24 h. By day 1, the children on Pc.R-ORS have gained more weight than G-ORS group. The weight changes are 2.13 ± 0.70 for Pc.R-ORS group and 1.64 ± 0.11 for G-ORS group. On day 2, these figures are 2.15 ± 0.69 and 1.74 ± 0.34 respectively for Pc,R-ORS group and G-ORS group. A few data are available to calculate weight change on day 3.

TABLE 19. **WEIGHT CHANGE OF CHILDREN DURING THE OBSERVATION DAYS FOR CASES USING ORS SOLUTION**

DAYS		RICE-ORS	GLUCOSE-ORS
DAY-1	N	61	61
	Mean	2.13	1.64
	±SD	0.70	0.11
DAY-2	N	31	53
	Mean	2.15	1.74
	±SD	0.69	0.34
DAY-3	N	10	30
	Mean	Data not enough	

18. DISCUSSION

This is a randomized controlled trial. It has strictly followed the inclusion and exclusion criteria. As a result the study has randomly selected homogeneous subjects. The baseline confounding variables are controlled through stratification on dehydration status and age of the children. Nutritional status, pre-admission diarrhoea period and stool frequency are controlled through screening criteria. As a result these variables are comparable between two groups at the beginning of study. The drop-out is nil. Only 2 cases from each group are non-cooperative during study period. Because their parents are not satisfied with the only treatment of ORT and demanding other medications. It is not possible to follow-up these cases because their parents quitted the hospital with discharge on risk bond (DORB).

The study cannot compare the Pc.R-ORS with a gold standard ORS. Only the WHO recommended standard G-ORS is available. Thereby, the study compared Pc.R-ORS with G-ORS. Both the ORS solution are randomly given to the randomly selected homogeneous subjects. The study is not blinded, since it is not possible to blind any body

involved in the study, as R-ORS is easily identifiable. Almost all the cases in both groups comply with the treatment regimens as per criteria and with the provision of equal feeding encouragement.

While the original hypothesis was to investigate if packaged precooked R-ORS with low glucose polymer would be viewed as efficacious as standard packaged G-ORS under clinical setup. This study demonstrates superiority when used with some or no dehydrated acute diarrhoeal children. By day 3, 82.8 % cases are recovered in Pc.R-ORS group and 60.9 % in G-ORS group (P: .005). Investigating the alternative hypothesis of proportion of recovery by day 3 for Pc.R-ORS and G-ORS, $1-\alpha$ is 2.75 and is much greater than 1.96. This true difference of recovery rate by day 3 may not be due to chance variation in two groups. And the sample size is enough to detect the true difference. These findings are strengthened by the cumulative recovery rate (Figure 3). Tracing backwards from day 3 to day 2, the cumulative rate of recovery by day 2 is 79.7% cases on Pc.R-ORS while only 42.2% of those on G-ORS. Further backwards, a greater divergence is seen. By day 1, 43.8% cases have recovered on Pc.R-ORS and 9.4% on G-ORS. And these differences by day 2 and day 1 are highly significant (P: .00001) in comparison

to day 3 (P: .005). If this true difference is rejected, there is less than 5% chance of rejecting a true difference of recovery for Pc.R-ORS than standard G-ORS.

This finding of better recovery for Pc.R-ORS is further justified by shorter duration of diarrhoea during the intervention period. This figure is 43 hours for Pc.R-ORS group and is less than G-ORS group (60 hours) and both groups entered with a history of equivalent pre admission diarrhoea period (43 hours). These results are also seen in previous clinical studies with R-ORS[12 15 35-39] but not with packaged Pc.R-ORS having high glucose polymer[16]. The biochemical mechanism is that, rice has 10 mmol/l and glucose has 111 mmol/l of osmolarity, i.e increasing the mmol/l increases the osmotic diarrhoea. The Pc.R-ORS having high glucose polymers (56%). But this study used Pc.R-ORS having low glucose polymer and its osmotic activity remains almost equivalent to R-ORS. By definition - failure of ORS solution intervention includes the cases of diarrhoea continue more than 3 days, referred for complication related to ORT, non-cooperation and non-compliance. Statistical significance are not found due to a few number of cases are recorded against referral, non-cooperation and non-compliance.

Meta-analysis[46] of the clinical trials that tested R-ORS with dehydrated children has demonstrated a mean stool output reduction rate of 18% in non-cholera cases and 36% in cholera cases. Stool volume increases with increases purging rate due to increased output of water and electrolytes with stool. So, the diarrhoeal stool is not a formed stool. This study used non-cholera cases and observed recovery rate as primary outcome variables. The recovery of diarrhoea is determined from the number of purging and stool consistency. In this study diarrhoea recover means that 0-2 formed stool in 24 hours with a point of recovery. Number of motions is an objective variable and confirmed by pre weighted tagged towel count with recording of time in hour. Stool consistency is a subjective variable and depends on the experience and perception of the observer. The study assigned the doctors who had 3-4 years of experience of clinical child health care and also trained for 2 weeks and their reliability tests result ares more than 90%.

The G-ORS group consumes more ORS solution than Pc.R-ORS group consume. And there is a remarkable down trend intake of ORS solution from day 1 to day 3 in both groups. The Pc.R-ORS group maintains a stable amount of food intake

(more than 40 ml/kg/24 h) than G-ORS group. On entry into study, the onset of food intake is 2.42 ± 1.54 h for Pc.R-ORS group and 2.72 ± 1.73 h for G-ORS group. This difference is comparable.

In this study, Pc.R-ORS group shows less stool output (ml/kg/24 h) than G-ORS group (28 ml vs 40 ml) on day 1, (23 ml vs 31 ml) on day 2 and (24 ml vs 33 ml) on day 3 of observation. The Pc.R-ORS group has passed more formed stool than G-ORS group. These findings are 38% vs 16% on day 1, 70% vs 43% on day 2 and 40% vs 42% on day 3 respectively for Pc.R-ORS and G-ORS group. On an average of 3 days observation, the stool frequencies are significantly higher for G-ORS group as opposed to Pc.R-ORS group. These data validated the better recovery and shorter duration of diarrhoea cases in Pc.R-ORS group than G-ORS group.

Corresponding to the less stool output, Pc.R-ORS group shows less stool frequency, more formed stool, less ORS solution intake, more food intake. Thereby, Pc.R-ORS group showed earlier and more rehydration, and more weight gain than G-ORS group. But urine output is not increased in Pc.R-ORS group than G-ORS group. Probably, G-ORS group used more ORS solution. The impact of ORS on vomitus is not

comparable, probably the study included only cases with no and some dehydration. And a few cases developed vomiting, probably both groups followed the treatment regimens strictly. Or the sample size is not enough to detect the impact on vomitus.

The result of the study will help to replace the currently used R-ORS with the Pc.R-ORS in clinical practice. More studies needed concerning choleric diarrhoea, cost-effectiveness and logistic constraints before recommendation for field supply.