Attachment 1. Date 07.3.93 19/4/93

(FACE SHEET) ETHICAL REVIEW COMMITTEE, ICDDR,B.
DR. M. HAFIZUR R. CHOWDHURY

Principal Investigator DR. MD. YUNUS Trainee Investigator (if any) ×

Application No. 93-013 Supporting Agency (if Non-ICDDR,B) ____

Title of Study EFFICACY OF BISMUTH-SUB SALICYLATE IN PREVENTING ACUTE DIARRHOEAL ~~EPISODES FROM BECOMING PERSISTENT IN RURAL~~ BANGLADESHI CHILDREN

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:
   ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   ___ Informed consent form for subjects
   ✓ Informed consent form for parent or guardian
   ✓ Procedure for maintaining confidentiality
   ✓ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

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

HRahman
Principal Investigator

Trainee

ENTERED 2 1 JUN 1993

EFFICACY OF BISMUTH-SUBSALICYLATE IN PREVENTING ACUTE DIARRHOEAL EPISODES FROM BECOMING PERSISTENT IN RURAL BANGLADESHI CHILDREN

PRINCIPAL INVESTIGATORS
DRS. M. HAFIZUR R CHOWDHURY & MD YUNUS

MATLAB HEALTH AND RESEARCH CENTRE
INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASES RESEARCH, BANGLADESH

SECTION 1: RESEARCH PROTOCOL

1. Title	:	Efficacy of bismuth-subsalicylate in Preventing acute diarrhoeal episodes from becoming persistent in rural Bangladeshi children.
2. Principal Investigators:		Dr. M. Hafizur R. Chowdhury Dr. Md. Yunus
3. Co-Investigators	:	Drs. E. H. Khan, K. Zaman, A. Rahman
Consultants	:	Dr. R. B. Sack
4. Starting date	:	As soon as possible
5. Completion date	:	15 months from starting date
6. Total direct cost	:	US$129,742.00
Possible Source of funding	:	

Signature of Divisional Head

ABSTRACT SUMMARY:

A double blind randomized clinical trial is being proposed to investigate whether treating patients with acute watery diarrhoea with bismuth-subsalicylate (BSS) in a dose of 100 mg/kg. day for 5 days, will prevent these episodes from becoming persistent, i.e, lasting 14 or more days. Twelve hundred and forty children aged 4-36 months of both sexes, hospitalized with the history of acute watery diarrhoea, will be divided into two groups. One group will receive BSS and the other a placebo. The efficacy of the BSS in the prevention of persistent diarrhoea will be compared between the treatment and placebo group. During the hospitalization, the physical examination and the number and consistency of the stools will be monitored. All patients will be kept in hospital at least five days to ensure intake of BSS. After the patients are discharged from the hospital following cessation of diarrhoea, they will be followed up at home on the 4th day after discharge to determine whether the current episode has resolved. Those patients leaving the hospital before cessation of diarrhoea who have received 5 days of therapy will be followed up at home on alternate days upto 14 days from the onset of diarrhoea to determine whether the episode becomes persistent. This research may generate new information regarding the prevention of persistent diarrhoea and may help in formulating better therapeutic strategies for the prevention of persistent diarrhoea.

SECTION 11: RESEARCH PLAN

A. Purpose of the trial

1. General objective:

The objective of the study is to evaluate the role of bismuth-subsalicylate in the prevention of persistent diarrhoea in Bangladeshi children aged 4-36 months.

2. Background:

Children under 3 years of age in the developing countries may experience as many as 10 episodes of diarrhoea per year, although the average number is 3-4 (1,2,3). Most diarrhoeal episodes are of relatively shorter duration (i.e. less than 7 days) and can be treated effectively with oral rehydration therapy and continued feeding with an appropriate diet. A subset of diarrhoeal episodes, however, continues for 14 days or more; these are referred to as persistent diarrhoea (2,3). Studies in several countries have shown that 3-20% of acute diarrhoeal episodes in children under 5 years of age become persistent (3,5). A prospective cohort study conducted in rural Bangladesh revealed that 8% of acute diarrhoeal episodes became persistent with the highest incidence in infancy (2). Episodes of persistent diarrhoea are often associated with deterioration in nutritional status and there

is a substantial risk of death (3). Although only a small fraction of acute diarrhoeal episodes become persistent, they are more likely to be associated with adverse outcomes. For example in rural Bangladesh during 1986-87, persistent diarrhoea was associated with 63% of all diarrhoea-associated deaths and 34% of all deaths in children under five years of age (4). Similar findings have been reported from Brazil, Peru, North India and Nepal (3,5,6). Viewed in another way, the study in northern India showed that although only 5% of all diarrhoeal episodes become persistent, 14% of such episodes ended fatally compared with less than 1% of episodes of shorter duration (5).

It is important to determine the possible risk factors for persistent diarrhoea and define better interventions in order to improve the morbidity and mortality of this diarrhoeal syndrome.

There is a substantial clinical evidence that bismuth-subsalicylate (BSS) is effective in the management of diarrhoeal disease, including treatment and prevention of travelers' diarrhoea (13). DuPont et al demonstrated among travelers that BSS reduces the frequency of unformed stool, improves stool consistency and decreases the accompanying symptoms of nausea and abdominal cramps (13). Soriano et al

reported that children with acute diarrhoea who were treated with BSS had significant reduction in stool frequency, duration of diarrhoea, hospital stay, stool weight and an improvement in stool consistency and general well being (14,15). Gryboski et al reported that BSS treatment children with chronic diarrhoea was associated with fewer and firmer stools with less water and significant clinical improvement (16). Several studies have indicated that BSS is well tolerated and is not associated with major adverse effects (13-17). Recently one study in Lima, Peru (personal communication) observed significant reduction in stool volume by 30%, duration of diarrhoea by 25% and duration of hospital stay by one day. Diarrhoea remained prolonged for more than five days after admission in placebo group in 23% children ($p<0.005$), three times as frequently as in the low dose (6%) or high dose (7%) BSS group. This finding suggested the possibility that BSS may prevent the development of prolonged diarrhoea. The reduction in stool volume was observed only from the third day of therapy. This pattern of late reduction in diarrhoeal stool volume is unlike that observed with the cereal based oral rehydration therapy where the reduction in the stool volumes occurred during the early period, usually during the first 24 hours (21). This finding appears to suggest that the mechanism of action of BSS is not an immediate antisecretory effect but is probably through the improvement

of gut epithelial healing and subsequent restoration of absorptive function of the small intestine or through an anti-inflammatory action which requires time to be effective. Due to this probable mechanism and other modes of action of BSS as described in the following section, we are hypothesizing that BSS may play an important role in preventing acute diarrhoeal episodes from becoming persistent. Therefore, we are proposing to undertake this study in Matlab Diarrhoea Treatment Centre.

BISMUTHSUBSALICYLATE (BSS)

Bismuth-subsalicylate is a compound of bismuth and salicylic acid but as the exact stiochiometry of the compound is unknown, it is designated subsalicylate. In the stomach bismuth- subsalicylate is hydrolyzed to bismuth oxychloride (which is soluble at acid pH and becomes a bismuth oxide/hydroxide mixture in the alkaline intestinal contents) and salicylic acid (which is poorly soluble at acid pH but is soluble in intestinal contents). Several studies have reported that after hydrolysis of bismuth subsalicylate in the gastrointestinal tract, measurable concentrations of salicylate in serum are achieved but bismuth is minimally absorbed. Serum levels of salicylate and bismuth, however, were well below the levels considered toxic (13-17). Several epidemiologic studies have suggested an association between

Reye's syndrome and the use of salicylate in general. Soriano et al (15) before starting their study, carefully reviewed all available data and found no association of Reye's syndrome with the use of BSS and other non-acetylsalicylic acids. This conclusion was supported by two reports from the institute of Medicine of the U.S. National Academy of Sciences and by the U.S. Food and Drug Administration. Bismuth or nondissociated bismuth appears to be strongly associated with the mucosal surface of the stomach. This association of bismuth with the gastric mucosal surface may be responsible in part for the cytoprotective properties of bismuth. In the colon nondissociated BSS and other bismuth salts are believed to react with hydrogen sulfide produced by anaerobic bacteria to produce bismuth sulfide, a highly insoluble black salt responsible for the darkening of stool during the use of BSS. This is transient and harmless and does not interfere with standard tests for occult blood. The mechanism of action of BSS in the treatment of diarrhoea is not completely understood. However possible explanations include; (18-20)

a) Prevention of attachment of organisms to the intestinal mucosa.

b) Direct antimicrobial effects on diarrhoeal pathogens.

c) Inactivation by binding of enterotoxins.

d) Anti-inflammatory effects of the salicylate component of BSS due to an inhibitory effect on prostaglandin synthesis.

e) Mucosal cytoprotective properties of the BSS.

f) Binding to bile acids that may contribute to diarrhoea.

BSS is able to bind bacteria of diverse species and these bound bacteria are subsequently killed (18). Soriano and co-workers observed in a clinical study that BSS was associated with clearance of pathogenic Escherichia coli from stool in 100% of cases but elimination of Rotavirus was not significant (14, 15). Cliodna et al found that BSS was significantly associated with clearance of Helicobacter pylori (22). Ericsson and co-workers have shown that BSS can inactivate the enterotoxins of Escherichia coli and Vibrio cholerae 01 and reduce toxin mediated fluid accumulation by 78% and 91% respectively in adult rabbit ligated intestinal loops (19).

3. RATIONALE:

Persistent diarrhoea is associated with significant infant and child mortality. Its adverse nutritional effects may contribute to the development of marasmus or kwashiorkor and surviving children are likely to show evidence of stunting (3). Management of persistent diarrhoea is difficult, challenging and time consuming. The main principles of management involve maintaining hydration and nutritional status with a suitable diet, until the intestinal damage is repaired. Due to known multimodal actions, including the probable gut healing mechanism of action of BSS, it is hoped that treatment of acute diarrhoeas with BSS may prevent these episodes from becoming persistent. If BSS is found effective, this will help formulation of better therapeutic strategies for the prevention of persistent diarrhoea.

B. Specific objectives:

1. To determine if BSS administered in a dose of 25 mg/kg every six hourly for five days is effective in the prevention of persistent diarrhoea.

C. Method of Procedure:

1. Inclusion criteria:

Patients from the demographic surveillance area, aged 4-36 months of either sex, with a history of acute watery diarrhoea of less than 72 hours duration and three or more watery stools in the last 24 hours, will be considered eligible for the study.

2. Exclusion criteria:

a) - Duration of diarrhoea more than 72 hours.

b) - Use of antibiotics within the previous 48 hours.

c) - Presence of gross blood in the stool on inspection.

d) - Weight for age less than the 5th percentile (National Centre Health Statistics)

e) - Acute diarrhoea associated with severe systemic infections like septicaemia, meningitis, pneumonia etc.

f) - Known Intake of salicylate in the last 24 hours.

g) - Allergy to salicylate.

h) - Attack of chicken pox within 90 days.

i) - Patient once included in the study

3. Outcome variables:

The study will compare the incidence of persistent diarrhoea between treatment and placebo groups. An episode will be considered persistent when diarrhoea continues for 14 or more days after onset. The following variables will be compared.

- number of stools per day throughout the course of illness.
- Stool consistency measured eight hourly.
- Daily body weight.
- Duration of diarrhoea after admission, - the time in hours from initiation of the study until passage of the last liquid stool prior to two formed stools or prior to 12 hours during which no stool is passed.
- Side effects will be monitored.

A diarrhoeal episode will be considered resolved when the patient has passed formed stools for three consecutive days.

4. ESTIMATE OF ELIGIBLE SUBJECTS:

About 7000-10,000 patients attend Matlab Diarrhoea Treatment Centre annually with 20% and 30% of the patients being infants and children 1-4 years of age respectively. (ICDDR,B Annual Report, 1985-86). About 50-55% of patients come from the demographic surveillance area and the rest from peripheral areas. In an analysis of admission data from the Matlab Diarrhoea Treatment Centre it was found that admission due to acute watery diarrhoea occurred in 81% of infants and 64% of children 1-4 years of age (10).

AGE (YEARS)	HOSP. (YEARLY)	ADMISSION FOR ACUTE WATERY DIARRHOEA(YRLY)	DAILY ADMISSION FOR ACUTE WATERY DIARRHOEA
<1 yrs.	800	570	1 - 2
1-4 yrs.	1200	676	1 - 2

Expected figures taking into account the exclusion criteria;

1. Complicating infections; 10% (23)
2. Refusal rate 2% (according to medical personal)

Sample size calculation:

We are expecting that 8% of the acute diarrhoeal episodes will become persistent in the control group as per findings of a prospective cohort study conducted in rural Matlab Bangladesh (2). We estimate that BSS will reduce by 50% the development of persistent diarrhoea i.e. 4% of the acute diarrhoeal episodes will be persistent in the treatment group. We will compare failure rates, using the following formula for calculation of sample size.

$$n = \frac{P^1 \times (100-P^1) + P^2 \times (100 - P^2)}{(P^2 - P^1)^2} \times \text{factor for}$$

Where P^1=8% = the percentage of failure rate i.e. proportion of patients who will develop persistent diarrhoea in the control group.

p^2=4% = the percentage of failure rate i.e. proportion of patients who will develop persistent diarrhoea in the BSS treated group.

$$n = \frac{8 \times (100-8) + 4 \times (100-4)}{(4-8)^2} \times 7.9$$

$$n = \frac{8 \times 92 + 4 \times 96}{16} \times 7.9$$

= 553, this calculation is made taking 7.9 as the factor for the significance level .05 and the power of 80%.

With an allowance of 10% drop out and 2% refusal, 620 patients in each group will detect our expected difference.

5. BASELINE EXAMINATION:

A baseline history and physical examination will be obtained to determine the subjects eligibility for inclusion in the trial and to collect relevant data prior to beginning the study that will allow comparison of the study groups after randomization. The baseline history and examination will include identification of the patients, a description of symptoms prior to admission and the duration, details of any treatment given for the illness, any recent history of diarrheoal illness and measles,

a description of the feeding status prior to admission, a description of stool prior to admission, the results of physical examination including the state of hydration, and nutrition determined according to standard criteria. The above information will be recorded on pre-designed and pre-tested forms.

6. INFORMED CONSENT:

If the patient is found to be eligible for inclusion in the study, an written informed consent will be obtained.

7. ALLOCATION TO TREATMENT GROUPS (RANDOMIZATION)

The patients will be randomly allocated to treatment groups using methods that avoid bias (see below). The test agent and the placebo will be packaged in identical containers. The medicines will be identical in appearance, flavour and volume. The containers will be arranged and numbered sequentially corresponding to the randomization. The randomization code will be according to a randomization list prepared using the block randomization technique with a variable block length of six to ten patients to avoid bias. The randomization list will contain more patients than the estimated sample size to allow for patients that leave the study prematurely. The level on the containers will contain only the name of the study and the serial number of the patient for which the container will be used. When a new patient is selected for the study e.g. the 10th patient, he or she will be assigned the medicine in container

number 10. Master randomization lists will be prepared by a responsible and trained person who is not otherwise associated with the study and will be kept in two independent places. The concentration of the test drug and the placebo will be adjusted in such a way that will permit administration of both test and placebo drugs in equal volumes.

8. CASE MANAGEMENT:

Drug treatment will commence after obtaining baseline data which will include history and physical examination, stool or rectal swab for culture & antigen detection (Salmonella, Shigella,V. cholerae, Rotavirus, E. coli), stool microscopy (entameba histolytica), stool for reducing substance for all before therapy as well as again for those who will continue diarrhoea after 13 days since its onset and weight, height/length. Patients will receive standard treatment with rice based ORS to correct dehydration. When needed patients will be treated with intravenous acetate fluid. An appropriate antimicrobial will be given to the patient when stool cultures or microscopy reveals organism such as V. cholerae, Shigella, or Entamoeba histolytica for which treatment is appropriate. Food will be offered appropriately for age at regular intervals commencing within 4 hours after admission. Test drug and placebo will be administered orally every six hours for five days. The patients

will receive BSS 100 mg/kg.day or placebo in liquid form. The volume of medicine (BSS or Placebo) to be given to each child will depend on body weight. Each bottle will contain maximum volume for the given age group. All patients will be kept in hospital for five days irrespective of diarrhoeal status in order to ensure five days of therapy. After the patients are discharged from the hospital after cessation of diarrhoea, they will be followed up at home on the 4th day after discharge to determine whether the current episode has resolved or not as per our definition of diarrhoea. Those patients who leave the hospital before cessation of diarrhoea but who have received 5 days' of therapy, will be followed up at home on alternate days upto 14 days from the onset of diarrhoea to observe the course of the current episode.

9. WITHDRAWALS FROM THE STUDY AND TREATMENT FAILURE:

If a patient develops a complication which prevents the planned treatment to continue, the patient will be withdrawn from the study and will not be considered for analysis e.g. paralytic ileus, septicaemia, pneumonia, meningitis etc. If a patient leaves the hospital before 5 days of therapy, he will not be considered in analysis. Any patient who leaves the hospital before cessation of diarrhoea and before 5 days of therapy have been given will not be considered in the analysis. Treatment will be considered a failure if diarrhoea has not stopped within 14 days' duration since onset.

10. ORGANIZATION OF THE TRIAL:

The patients will be selected from the Matlab Diarrhoea Treatment Centre if they fulfill the inclusion criteria. The Principal Investigators with the assistance of a full time medical officer will take care of all patients. Eight-hourly evaluation will be recorded on a pre-designed form. Patients will be enrolled in the study among those seen in the morning upto 11 am to enable a convenient 8 hourly schedule. The number of stools will be recorded using open diapers. Stool consistency will be determined and recorded as follows: "liquid" if it can be poured, "soft" if it acquires the shape of the container and "formed" if it retains its own shape. Daily body weights will be taken at 24 hours interval from admission. Other clinical parameters like fever, vomiting, stool and urine mixed volume, ORS and plain water intake, amount of intravenous fluid infused will be monitored and recorded 8 hourly as per the routine practice of the hospital.

Study Requirements:

Existing hospital equipment will be adequate for monitoring the study patients, except that one new paediatric balance (weighing machine) will also be required.

Staffing:

1. PIs (Dr. Hafiz 50% and Dr. Md. Yunus 20% of time)
2. Medical Officer (Research fellow) - Two
3. Senior Staff Nurse --- --- --- Two
4. Data Processing Assistant --- --- One
5. Community Health Workers --- --- Two

The above staff members will have to be recruited for monitoring the patients in the hospital as well as in the field and for data entry into the computer.

Timetable:

The study is expected to extend over a 15 months period. Since much of information is routinely obtained, there should be no difficulty in entering three children daily into the study. Final analyses and report writing will be undertaken as soon as possible after completion of the study.

Data analysis:

The pre-intervention data on admission like age, sex, duration of diarrhoea, state of dehydration, vomiting, fever, weight for height etc. will be compared between the treatment and placebo group. Success rates in terms of prevention of persistent diarrhoea will be compared between the treatment and placebo group using the standard chi-square test. Also the length of illness in the two groups - means/medians analysis according to etiological agent will be detrmined.

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DETAILED BUDGET

PERSONNEL		IN US DOLLAR
Dr. Hafiz R. Chowdhury	1 x 9m x 750 =	6,750.00
Dr. M. Yunus	1 x 3.6mx 1742=	6,271.00
Medical Officer (Research Fellow)	2 x 36m x 180 =	5,400.00
Nurses (GS5 Step1)	2 x 36m x 379 =	11,370.00
Data Processing Assistant (GS4 ST1)	1 x 18m x 305 =	4,575.00
Community Health Worker	2 x 36m x 75 =	2,250.00
		36,616.00

PATIENT HOSPITALIZATION:

1240 Patients: Extra 2 days stay x US$12.50/day (Cost of routine 3 days stay will be covered by Matlab Diarrhoea Treatment Centre)	31,000.00

LABORATORY

Stool for Routine Microscopic Examination (1240 tests @US$1.65)	2,046.00
Rectal Swab for Salmonella, Shigella, Vibrios (cost will be covered by Hospital Surveillance)	
Rota virus, (1240 x US$ 4.58)	5,680.00
E. Coli- Pick & Pool of 5 colonies (1240xUS$ 2.75)	3.410.00
ETEC (LT,ST). EAEC EIEC Testing (Us $ 330 per 100 samples, 13 x 330)	4,290.00
Miscellaneous investigations	1,000.00
	16,426.00

OTHERS

Bismuth subsalicylate	-	1,000.00
Supplies & Materials	-	1,000.00
Child Weighing Machine	-	2,000.00
Personal Computer	-	3,000.00
Printing & Publication	-	1,000.00
Xerox	-	100.00
Transport (Local Travel)	-	1,500.00
International Travel	-	3,000.00
Data Management (Computer)	-	4,000.00
Staff Clinic	-	200.00
Medical Illustration	-	200.00
		15,000.00

SUMMARY SHEET

BUDGET PROPOSAL

Programme Name: Bismuth-Subsalicylate and Prevention of Persistent Diarrhoea.

Principal Investigators: Drs. Hafizur Rahman Chowdhury & Md. Yunus

Expenses category

Personnel	=	US$	36,616.00
Patient hospitalization	=		31,000.00
Laboratory	=		16,426.00
Others	=		15,000.00
Total direct costs	=		99,040.00
Overhead cost (31 %)	=		30,702.00
TOTAL COSTS	=		129,742.00

ICDDR,B MATLAB HEALTH & RESEARCH CENTRE

BISMUTH-SUBSALICYLATE AND PREVENTION OF PERSISTENT DIARRHOEA

IDENTIFICATION FORM

Has verbal consent been obtained ? Yes=1 No=0 [ ]

Child's Name Sex Male=1 Female=2 [ ]

CID No. of Child [ ][ ][ ][ ][ ][ ][ ][ ][ ]

Village Family Individual

Informer's Name and Relation

Mother=1
Father=2
Others=3 [ ]

Date of birth [ ][ ][ ] Family Members No. [ ][ ]

dd mm yy

Date of admission to study : [ ][ ][ ]

dd mm yy

Time of admission to study : [ ][ ]

hh mm

Presenting complaints

1) Duration

2) "

3) "

History of present illness -

History of past illness -

1. Recent history of diarrhoea (within 90 days) Yes=1 No=0 [ ]
2. If yes, Type of diarrhoea [ ]
   1=Watery/liquid, 2=Mucoid 3=Blood mucoid.
3. Recent history of Measles. Yes=1 No=0 [ ]
   (within 45 days)
4. History of chicken pox Yes=1 No=0 [ ]
   (within 90 days)
5. Other illness describe with duration

Socio-economic history-

Feeding history- [ ]

Fully breast feed----------1

Partially breast feed--------2
(BM and cow's or formula)

Formula or cow's milk only --3

Mixed feed----------4
(any milk and other food)

DPT: No=0, Yes Complete=1 [ ]

Yes, incomplete=2
Don't know=9

OPV: No=0 Yes Complete=1 [ ]

Yes, incomplete=2
Don't know=9

Measles: No=0 Yes Complete=1 [ ]

Don't know=9

BCG: No=0 Yes=1 [ ]

Don't know=9

Vitamin A before admission : Yes=1 No=0 [ ]

If yes, duration (days) [ ][ ]

Drugs received before admission, if any:

1)

2)

3)

General examination on admission

Appearance -

Pulse (per m.)-

Temperature(F)-

Respiration (pm)-

Dehydration -

Anaemia -

Jaundice -

Oedema -

Eyes -

Ears -

Tonsils -

Weight (kg) -

Height (cm) -

MUAC (mm) -

Wt. for age (NCHS)-

Wt. for Ht. (NCHS)-

Tongue-

Hair-

Skin-

Lymph nodes-

Others -

CHEST

Heart -

Lungs -

Rib indrawing -

ABDOMEN

Size & Shape-

Bowel sounds-

Spleen-

Kidney-

OTHER IMPORTANT FINDINGS (IF ANY)-

STATUS DURING ADMISSION

tudy Patient No. [ ][ ][ ]

) Age (Months) [ ][ ]

) Sex (1=M 2=F) [ ]

) Body Weight (kg) - [ ][ ][ ]
(last box for decimal)

) Height (cm) (last box for decimal) [ ][ ][ ][ ]

) MUAC (mm) [ ][ ][ ]

) Duration of diarrhoea (days) [ ][ ][ ]

) Frequency (No. per 24 hours) [ ][ ]

) Stool Consistency 1=Watery/Liquid
2=Loose/Soft 3=Semi Solid 4=Solid 5=Others [ ]

) Stool Character 1=Normal 2=Yellow Liquid
3=Mucoid 4=Blood Mucoid 5=Black 6=Others [ ]

0) Vomiting at home (before admission)
Yes=1 No=0 [ ]

1) If yes, duration (Hours) [ ][ ]

2) Status of Dehydration,
1=Mild 2=Moderate 3=Severe 0=None [ ]

3) Temparature (F) (Last box for decimal) [ ][ ][ ][ ]

4) Anorexia, Yes=1 No=0 [ ]

5) Tongue 1=Clear 2=White Coated
3=Black Coated [ ]

6) ORS Intake before admission Yes=1 No=0 [ ]

17) Recent diarrhoeal history Yes=1 No=0 ☐
(Within 90 days)

18) If yes, type of diarrhoea 1=Liquid/Watery ☐
2=Mucoid 3=Blood Mucoid

19) Recent Measles History Yes=1 No=0 ☐
(Within 45 days) Don't know=9

FEATURES DURING STUDY

Child Study No: [ ][ ][ ][ ] [ ][ ][ ] [ ][ ]

Day:

01) Weight in kg at 8:45 am [ ][ ][ ]

02) Stool Passed today Yes=1 No=0 [ ]

03) Frequency (No. since 8 am today) [ ][ ]

04) Consistency 1=Watery/Liquid 2=Loose/Soft
3=Semi Solid 4=Solid 5=Others [ ]

05) Characters 1=Normal 2=Yellow Liquid
4=Blood Mucoid 5=Black 6=Others [ ]

06) Vomiting Yes=1 No=0 [ ]

07) Frequency (No. since 8 am today) [ ]

08) Anorexia today Yes=1 No=0 [ ]

09) Fever Yes=1 No=0 (^{o}F) [ ]

10) Tongue, 1=Clear 2=White Coated
3=Black Coated [ ]

11) ORS Intake (ml/kg) (Since 8 am today) [ ][ ][ ]

12) Intravenus Fluid Infusion (ml/kg)
(Since 8 am today) [ ][ ][ ]

13) Stool mixed urine (ml/kg)
(Since 8 am today) [ ][ ][ ]

CONSENT FORM

Diarrhoea is one of the biggest killer of under five children in Bangladesh. Recent studies have shown that BSS is effective in the management of Acute Watery Diarrhoea and also suggested that it may prevent acute diarrhoeal episode becoming persistent. ICDDR,B Matlab Health and Research Centre has been conducting study to see the role of BSS in the prevention of persistent diarrhoea. For the purpose of the study a dose of BSS will be administered to half of the study children and rest half will get placebo and outcome will be followed up during hospitalization and at houses in definite days after discharge from the hospital. Several recent studies have indicated that BSS was not associated with any adverse side effect excepting black tongue and black stool. This black stool and tongue will be cleared after discontinuation of therapy. If BSS is found effective in our clinical trial, it will help informulating better therapeutic strategies for the management of persistent diarrhoea.

If you like to participate in our study, your child may be needed to stay in the hospital at least for five days irrespective of diarrhoeal status. Our staff members will follow-up those children on the 4th day after discharge following cessation of diarrhoea from the hospital to see whether the current diarrhoeal episode is ressolved or not. For those children who will leave hospital before cessation of diarrhoea but received five days therapy, will be followed-up at houses on alternate days for a total of 13 days since onset of diarrhoea to see whether the current episode is resolved or not.

If you don't like to participate in our study, your child will get possible treatment. You are at liberty to withdraw your child from the study at any time without any obligation and jeopardizing your medical care and treatment.

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

SIGNATURE OF THE INVESTIGATOR

DATE

SIGNATURE/LTI OF LEGAL GUARDIAN OF CHILDREN

DATE

সম্মতি পত্র

বাংলাদেশে ডাইরিয়া রোগ পাঁচ বছরের নীচের শিশুদের জন্য অন্যতম একটা ঘাতক ব্যাধি। সাম্প্রতিক বিভিন্ন গবেষণায় দেখানো হয়েছে যে BSS, সবল্প মেয়াদি তরল ডাইরিয়াতে খুবই কার্যকরী এবং ধারনা দেয়া হয়েছে যে ইহা সবল্প মেয়াদি ডাইরিয়াকে দীর্ঘ মেয়াদি ডাইরিয়া তৈরী থেকে রক্ষা করতে পারে। দীর্ঘ মেয়াদি ডাইরিয়া প্রতিরোধে BSS এর ভূমিকা দেখার জন্য ICDDR,B মতলব স্বাস্থ্য এবং গবেষণা কেন্দ্র একটা গবেষণা পরিচালনা করছে। এই গবেষণার জন্য পরীক্ষাধীন শিশুদের অর্ধেককে একটা নির্দিষ্ট মাত্রায় BSS ও বাকী অর্ধেক শিশুকে Placebo খাওয়ানো হবে এবং হাসপাতালে থাকাকালীন সময় এবং হাসপাতাল থেকে ছুটির পরে একটা নির্দিষ্ট নিয়মানুযায়ী বাড়ীতে গিয়ে ইহার ফলাফল দেখা হবে।

সাম্প্রতিককালের বিভিন্ন গবেষণায় দেখানো হয়েছে যে জিবহবা ও পায়খানা কালো হওয়া ছাড়া BSS এর জন্য কোন পাশর্প্রতিক্রিয়া নেই। এই ঔষধ খাওয়া ছেড়ে দিলে পায়খানা ও জিবহবার কালো রং চলে যায়। এই গবেষণায় যদি BSS এর ফলপ্রসূ কার্যকারিতা প্রমানিত হয় তাহলে ইহা ভবিষ্যতে দীর্ঘ মেয়াদি ডাইরিয়ার চিকিৎসা ক্ষেত্রে সহায়ক হবে।

আপনি যদি আমাদের গবেষণা কাজে অংশ নিতে সম্মত থাকেন তাহলে আপনার বাচ্চাকে কম পক্ষে পাঁচদিন হাসপাতালে রাখতে হবে -- এমনকি ডাইরিয়া সেরে গেলেও। আমাদের কর্মীরা যে সমস্ত শিশুরা ডাইরিয়া ভাল হলে ছুটি হবে, তাদেরকে ছুটির চতুর্থ দিনে বাড়ীতে গিয়ে দেখবেন বর্তমান ডাইরিয়া পুরাপুরিভাবে ভাল হয়েছে কিনা। আবার যে সমস্ত শিশুরা পাঁচ দিনের ঔষধ পাওয়ার পর ডাইরিয়া ভাল না হয়েও হাসপাতাল থেকে চলে যাবে তাদেরকে, আমাদের কর্মীরা একদিন পর পর সর্বমোট ডাইরিয়া শুরু থেকে ১৩ দিন পর্যন্ত বাড়ীতে গিয়ে দেখবেন বর্তমান ডাইরিয়া পুরাপুরিভাবে ভাল হয়েছে কিনা।

আপনি আমাদের গবেষণায় অংশ নিতে সম্মত না হলেও আপনার শিশু সম্ভাব্য সকল চিকিৎসা পাবে। আপনি যে কোন সময় আপনার শিশুকে গবেষণা থেকে বিরত রাখতে পারেন এবং সেক্ষেত্রেও আপনার শিশুর চিকিৎসা ব্যহত হবে না।

আপনি যদি স্বতস্ফূর্ত হয়ে আমাদের গবেষণায় অংশ নিতে সম্মত হন তাহলে নীচে স্বাক্ষর করুন অথবা বাম হাতের বুড়ো আংগুলের ছাপ দিন।

গবেষকের স্বাক্ষর _____

তারিখ: _____

সাক্ষর/বৈধ অভিবাবকের বাম
বুড়ো আংগুলের ছাপ: _____
তারিখ: _____

File:C:\ABWS\CONSENT.HOS

C.V. OF DR. MD. HAFIZUR RAHMAN CHOWDHURY

01. Name : DR. MD. HAFIZUR RAHMAN CHOWDHURY

02. Date of birth : 2nd May, 1960

PROFESSIONAL TRAINING

01. Attended ICDDR,B training course entitled "Introductory guide to statistics, epidemiology and demography" from March 30 to June 15, 1986.

02. Attended a week long training course on Conjunctival Impressioncytology for assessing Vitamin-A from POSTGRADUATE INSTITUTE OF MEDICAL EDUCATION & RESEARCH CHANDIGARH, INDIA.

PROFESSIONAL EXPERIENCE:

01. Serving as a Medical Officer in ICDDR,B Matlab Health and Research Centre since 2nd February, 1986. Responsibilities include routine patient care in the hospital, MCH-FP Clinic as well as in the Staff Clinic. Also involved in research and training activities at Matlab.

02. Experienced in applying and reading Multi-test CMI among rural Bangladeshi children.

03. Experienced in taking and staining Conjunctival Impression Cytology to detect subclinical vitamin A deficiency.

RESEARCH ACTIVITIES:

01. I was actively involved in the training and field implementation of a Communtiy based cohort study entitle "Epidemiology of Persistent Diarrhoea in Bangladeshi Children", P.I.: Dr. A. H. Baqui.

02. Current Technical Supervisor of the Matlab Cause of Death Analysis.

03. Working as a Co-investigator in Measles Surveillance Study . P.I. (s): Dr. L.A. de Francisco.

PUBLICATIONS:

01. H.R. Chowdhury, V. Fauveau, M. Yunus, K.Zaman & A. Briend: Is acute watery diarrhoea an important cause of morbidity & mortality among rural Bangladeshi children? Transactions of The Royal Society of Tropical Medicine And Hygiene 1991, 85: 128-130.

02. Abdullah H. Baqui, Robert E. Black, R. Bradley Sack, Md. Yunus, A.K.M. Siddique, H.R. Chowdhury: Epidemiologic and Clinical Charactertistics of Acute and Persistent Diarrhoea in Rural Bangladesh. Acta Paediat Suppl. 1992, 381:15-21.

03. Abdullah H. Baqui, Robert E. Black, Md. Yunus, A.R. Azimul Haque, H.R. Chowdhury, R. Bradley Sack: Methodologic Issues in Diarrhoeal Diseases Epidemiology: Definition of Diarrhoeal Episode. Int. Journal of Epidemiology; 1991, 20: 1057-63.

04. Abdullah H Baqui, R Bradley Sack, Robert E Black, K Haider, A Hossain, A R M A Alim, M. Yunus, H.R. Chowdhury, A K Siddique: Enteropathogens associated with actue and persistent diarrhoea in Bangladeshi children under 5 years of age. Journal of Infectious Diseases, 1992; 166:792-96.