Attachment 1. Date Oct. 16, 1990

(FACE SHEET) ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr Amal K. Mitra

Trainee Investigator (if any) _____

Application No. 90-016

Supporting Agency (if Non-ICDDR,B) _____

Title of Study "Controlled trial of an energy dense porridge ..... with acute watery diarrhoea"

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 NA
   (d) Sensitive questions Yes (No) NA
   (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 NA
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 informa should be included in the abstract sum
   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.

Amal
Principal Investigator

Trainee

90-016
17/10

SECTION 1 - RESEARCH PROTOCOL

TITLE: Controlled trial of an energy dense porridge of rice or rice plus lentil, liquefied with added amylase rich germinated wheat cereal flour, in children aged 6 months to 23 months with acute watery diarrhoea.

PRINCIPAL INVESTIGATOR: Drs. Amal K. Mitra, Mujibur Rahaman

CO-INVESTIGATORS: Dr. F. C. Patra, Mr. M. A. Wahed

PROJECT CO-ORDINATOR: Dr. D. Mahalanabis

STARTING DATE: December 1, 1990

COMPLETION DATE: December 1, 1992

TOTAL DIRECT COST: US$ 134,199

POSSIBLE SOURCE OF FUNDING: UNICEF

SCIENTIFIC DIVISION:

This protocol has been approved by the Clinical Science Division

Signature of the Associate Director, CSD

Date: 16/10/90

8. ABSTRACT SUMMARY:

To evaluate the role of liquefied energy dense diet in increasing the calorie and nutrient intake in infants and young children aged 6 months to 23 months with acute diarrhoea, patients will be randomised to receive either of the three diets in the ICDDR,B hospital: i) the experimental group receiving an energy dense porridge of rice or rice plus lentil, liquefied by adding amylase rich germinated wheat cereal flour (group 1), ii) one control group receiving a semi-solid porridge of rice or rice plus lentil of same energy density (group 2), and iii) another control group receiving a porridge of rice or rice plus lentil, liquefied by adding water to the same viscosity as the diet of group 1 (group 3). A total of 99 patients of either sex, 33 in each group will be studied over a period of two years. Besides standard case management, four meals of the assigned porridge ~~(200 ml/kg/24 hours)~~ will be offered every day until discharge. The major response variables will be quantity of food intake (calories and macro-nutrients), quantity of breast milk intake, diarrhoeal duration, and diarrhoeal stool output. Net absorption of total energy, protein and lipids of 100 male patients will be measured using an intake and output balance over a period of three days.

REVIEWS:

a) Chairman, Research Review Committee:----------

b) Chairman, Ethical Review Committee:----------

c) Director, ICDDR,B:----------

SECTION II - RESEARCH PLAN

INTRODUCTION:

Objectives:

i) To evaluate the role of liquefied energy dense porridge preparations in increasing the calorie and nutrient intake in infants and young children aged 6 months to 23 months with acute watery diarrhoea.

ii) To measure the net absorption of total energy, protein and lipids in male infants and young children aged 6 months to 23 months with acute acute diarrhoea using an intake and output balance over a period of three days.

Background:

Appropriate feeding with adequate calories and nutrients is important component of case management of children with arrhoea[1]. The intake of food during diarrhoea may be diminished e to anorexia[2], and can be overcome by providing sufficient ount of nutritionally adequate weaning food. Unfortunately, ietary bulk" (high volume to make thin viscosity) remains a jor problem in the nutritional management of young children[3]. e high energy requirement of young children, together with eir limited stomach capacity, make it impossible for them to t enough of this food, particularly if the number of meals per

y is low[4]. Most mothers of low socioeconomic groups do not get ough time to feed their children more than 3-4 times a day[5]. A et that is high in bulk is common in most of the developing untries, including Bangladesh, where weaning foods are based inly on starchy staples, such as corn or rice[6]. It is, erefore, vital that simple means be established whereby the lorie density of traditional weaning foods may be enhanced ile maintaining a thin consistency.

Two examples of such traditional, bulk-reducing methods have tracted the attention of researchers: the first is sprouting alting or germination) of cereal (Brandtzaeg et Al. 1981; Mosha d Svanberg 1983) and of legumes; the second is fermentation. In rminated cereal flours, advantage is taken of the amylolytic zymes (developed during germination) to hydrolyse the starch anules into simple sugars that have a low water-binding and olding capacity. During this stage, the gruel liquefies, making ssible more solids per unit volume, while maintaining a thin nsistency (Brandtzaeg et al. 1981). Moreover, absorption from a rridge with added amylase rich germinated cereal flour (ARF) y be more efficient than a native porridge to which ARF has not en added.

Specific aims:

a) Does the use of a porridge liquefied by ARF to feed fants and young children with acute watery diarrhoea lead to creased intake of calorie and nutrients from food compared to) the same porridge in a semi-solid form without added ARF and erefore having a high viscosity, and (ii) the same porridge luted to the same viscosity as the experimental porridge with ter and therefore having a lower energy density ?

b) Is energy dense porridge liquefied with ARF more absorption ficient and therefore its use in children (aged 6 months to months) with acute diarrhoea leads to increased absorption of tal calories, proteins and lipids ?

c) Dose feeding with such a porridge have a negative effect on east milk intake ?

d) Does feeding with such a porridge have any effect on the urse of illness e.g. diarrhoeal duration and diarrhoeal stool tput (admission to 24 hours and admission to cessation of arrhoea) ?

RATIONALE / SIGNIFICANCE:

This study will assist in the development of a highly sorption efficient, inexpensive, locally available, energy nse diet for the use during acute watery diarrhoea in infants d young children. In addition, introduction of a suitable ergy dense weaning food during an illness could act as an entry

int for educating mothers on appropriate weaning practices.

RESPONSE VARIABLES:

Major:

1. Quantity of food intake (calories and macro-nutrients) daily and for the total duration of diarrhoea from the experimental porridge preparation on a realistic number of feedings per day.

2. Quantity of breast milk intake daily and during the total duration of diarrhoea (measured by weight difference before and after feeding using a precision balance).

3. Diarrhoea duration.

4. Diarrhoea stool output (0-24 hours and 0-cessation of diarrhoea).

5. Percent absorption of total energy, proteins and lipids.

condary:

1. Acceptance of the experimental porridge by the mothers as compared to the acceptance of unaltered porridge and diluted porridge.

METHODS AND PROCEDURES:

igibility criteria:

. Watery diarrhoea of less than 5 days duration prior to admission, and three or more watery stools in last 24 hours;

. children of either sex aged 6 months - 23 months; only males for the metabolic balance study;

. absence of associated systemic infections and/or complications;

. absence of severe malnutrition i.e. gross marasmus, kwashiorkor or marasmic kwashiorkor.

. parents are willing to give informed consent.

mple size:

Three groups of patients will be studied: the experimental oup receiving an energy dense porridge liquefied by adding ARF roup 1), one control group receiving a native semi-solid rridge of same energy density (group 2) and another control oup receiving the native porridge liquefied by adding water to e same viscosity as the energy dense liquefied porridge in the perimental group (group 3). The sample size is being calculated detect a difference between group 1 and group 2 in the antity of calorie and nutrient intake daily and for the total

riod of diarrhoea and a reduction in breast milk intake if any tween the two groups. Exploratory analysis will also be carried t to detect the differences between group 1 and group 3 for the tal energy and nutrient intake and impact on breast milk take.

We expect a 35% increase in total food intake daily in the perimental group. This is based on our unpublished data on food take from a single meal of energy dense porridge liquefied by ding ARF compared with a single meal of native semi- solid rridge of same energy density in infants aged 6 months to 12 nths. The mean quantity of porridge ingested by the group of fants given a energy dense porridge liquefied with ARF was gms and the mean intake in the control group receiving a semi- lid porridge of same energy density was 26 gms. With a andard deviation of 20 the sample size to detect the difference 5% level of significance and with a power of 80% was 28 in ch group. Therefore the total sample size for the three groups 84. To this we add 15 for deviated course and the total is 99. r comparison between group 1 and group 3 we note that a 17% rridge of rice needed to be diluted to 60% by adding water to e native porridge to make it similar in viscosity to the quefied porridge in the experimental group. We expect that the take from this liquefied porridge in group 3 will be at best e same as the intake from the experimental porridge liquefied

by adding ARF. Therefore the equivalent amount of the native porridge consumed will be about 24.6 gms in group 3 compared to 41 gms in group 1. With a standard deviation of 20 the sample size in each group is 24 i.e. a total of 72 for the three groups. We add 15 for deviated course and therefore the sample size is about 87 patients.

Sample size for the metabolic balance part:

Due to lack of information from any earlier studies it is difficult to calculate the sample size for this part of the protocol. If we assume that percent absorption of total energy from the control porridge is 60% and that from the experimental liquefied energy dense porridge is 85% then the calculated sample size at 5% level of significance and 80% power is approximately 47 patients per group. If we assume that 60% of the patients recruited will be males (based on the attendance at the treatment centre) then about a total of 60 patients will be recruited from the first part of the study. With an additional 40 male patients for the second part, a total of 140 children will be studied as an adequate sample. Sample size will be reviewed after 60 patients have been enrolled into the study and adjustments made.

nrolment of subjects:

Patients will be enrolled from the triage area of the Clinical esearch Centre (treatment centre) of ICDDR,B. Children ulfilling the eligibility criteria and attending between 8 am nd 12 noon on week days will be considered for inclusion into he study. Not more than 3-4 patients will be recruited each week o enable research staff to carry out all specified activities. ritten informed consents will be taken before entering a patient nto the study.

aseline examination:

A baseline history, physical examination and other social and nthropological data will be recorded on a pretested data form Annex 1). The baseline history and examination will include:

- identification of the subject;
- a description of symptoms prior to admission and their duration;
- details of any treatment given for the illness before admission;
- a description of the feeding status prior to admission, and also before the onset of illness;
- state of hydration according to WHO criteria;
- anthropometric measurements (recumbent length, body weight, mid upper-arm circumference, triceps skinfold thickness and tibial length).

Allocation to treatment group (randomisation):

Randomisation will only take place after a patient has been rehydrated, and irrevocably entered into the study.

The study cannot be blinded because the appearance of the three diet preparations are obviously different. Randomisation tables will be prepared using random permuted blocks of variable lengths. Separate randomisation list will be prepared for patients of either sex aged 6 mo - 12 mo and those aged 13 mo - 23 mo. Serially numbered sealed envelopes corresponding to the serial numbers of the patients to be recruited into the study will contain treatment allocation according to the randomisation code. Additional randomisation list and sealed envelopes will be prepared for another 40 male patients for the metabolic part of the study. After the patient has been irrevocably assigned to the study and admitted to the ward the sealed envelope containing the serial number of the study patient will be opened to ascertain the diet group the patient belongs to and the patient will be assigned to a treatment group accordingly.

The randomisation list and sealed envelopes will be prepared and kept by a responsible and appropriately trained person who is not otherwise associated with the study.

tandard case management and the experimental treatment:

No deviation from routine case management of the treatment entre will take place except for the type of food offered and he number of feeds will be standardised.

Initial rehydration will be done either by rice-ORS or IV cetate according to state of dehydration, and maintenance of ydration will be carried out with rice-based oral rehydration olution until the end of diarrhoea. The amount of ORS will be fered based on the state of hydration according to WHO iteria. Supplemental intravenous fluid therapy will be given in se of failure to achieve adequate rehydration within 8 hours om the initiation of therapy, or a worsening of the signs of hydration, despite intake of the estimated fluid requirement. fluids will also be given in case of reappearance of clinical gns of dehydration during the maintenance phase, or controllable vomiting during any phase of treatment.

Breast-feeding will continue and the babies will be weighed fore and after offer of breast milk. Mothers will be advised to port to the volunteers the approximate time of breast feeding. here is no relevent data regarding the frequency of breast eeding. For the nature of breast feeding, a spot survey was done ong the mothers of infants and young children (aged 6 months to months) admitted in the treatment centre of ICDDR,B. 76% 4/58) patients were partially breastfed, 4% (7/58) were total

reastfed and a remaining of 10% (17/58) were non-breastfed
nnpublished). In addition to the scheduled diet, an infant may
eed to give breast-feeding every 3-4 hourly and young children
-2 years) may need it even less frequent.

Immediately after initial hydration, the standardised diet
ill be offered, the composition and the method of preparation of
hich is attached (Annex 2). Four meals of assigned porridge will
offered daily (8-9 am, 1-2 pm, 4-5 pm, 8-9 pm); each time
orridge will be given ad lib before breast feeding for a maximum
eriod of 30 minutes. Mothers will feed their babies with spoon
nd cup under direct supervision of the volunteers. The assigned
iet will be continued until the patient is discharged (maximum 6
ays). At discharge, the mothers will be advised to feed their
abies as usual. Infants and children who are not breastfed will
eceive milk feeds; isocaloric milk mixture (artificial milk
ormula) will be given ad lib after the assigned meal is offered.
uring our use-experience of liquified porridge, we did not
ncounter with any untoward effects of the diet. Also there is no
nown side effects or risk of the experimental diet from the
revious studies. No medicines will be given to the patients
nless cholera or shigella species is detected on stool culture.

etabolic balance study:

The balance study will be done as described by Molla *et al*[9]. t will be initiated 24 hours after patients start taking the ssigned diet. Charcoal will be given as a marker at the start of he balance period and 72 hours later. Collection of stool and rine will be done after the appearance of the first marker and ntil that of the second one. Five ml of acetic acid will be put n the stool collecting pot to reduce bacterial growth and ermentation. All samples will be kept at -20°C before analysis.

aboratory procedures (routine):

1. Stool for microscopy on admission;
2. Stool for culture of *V. cholerae*, *shigella spp.*, and salmonellae on admission; E. coli colonies will be saved and tested for toxins;
3. ELISA for rotavirus on admission;
4. Blood for CBC, electrolytes and sp. gravity on admission and on the second day to assess hydration;
5. Urine, x-ray and blood C/S if required.

pecial laboratory procedures:

Aliquotes of stool samples from homogenised 72 h collection ill be taken and analysed for fat by Vande Kamer's method[7], itrogen by the micro-Kjeldahl method[8], and carbohydrates by ubtracting those from total energy. Total energy content will be

ermined by ballistic bomb calorimetry (Gallenkamp). Dietary
tents for fat, nitrogen, and viscosity of diets using a
cosimeter (Brookfield Engineering Labs, Massachusetts, USA),
amylase by cobas bio method will be analysed. Total urinary
rogen excretion per day will be determined. The coefficient of
estinal absorption will be calculated as:

[(Intake - loss)/intake]x100.

iated course of the study:

Patient will be withdrawn from the study in case of non-
pliance, either because the patient is removed from the
pital before the end of the study, or because the patient
uires unscheduled treatment for a serious intercurrent illness
g., pneumonia, meningitis) and the planned diet treatment can
be continued. In case of a serious illness, the patient will
moved to the Intensive Care Unit or to the inpatient area
ending on the nature of the problem, and appropriate
atments will be started. The scheduled diet will be re-started
soon as the patient can take normal diet. All records of the
ient's illness, period of discontinuation of diet and the
come of the patient will be noted and considered in the
lysis phase.

AL ORGANISATION:

ilities and patient population

With the present rate of attendance of infants and children h acute diarrhoea at the CRC there is an adequate number of ients available for recruitment into the study. The metabolic t kitchen will be responsible for preparing the diets under supervision of the weaning food laboratory. Patients for the abolic study will be kept in the metabolic ward where angements are available for intake-output balance studies. All er patients will be studied in the treatment centre.

hods for response variables

Intake of porridge will be measured by weighing the tainers before and after feeding. Total intake of porridge per and during the whole illness will be completed by combining se measurements. Because it will be impossible to mask the ntity of the study diets, the clinical measurements will be pleted by the study research assistant (nurse) who is unaware the children's dietary groups. Stool volume will be measured ry 8 hours using a pre-weighed polythene container put in a stic bucket. Stool output ($ml.kg^{-1}$) from 0-24 hours and from our to end of diarrhoea will be computed. Urine volume will be lected in paediatric urine collector for male children. Vomits l be captured in preweighed towels. Duration of diarrhoea will

e measured from admission into the study (the time of andomisation) to cessation of diarrhoea. ORS intake will also be easured during the illness and computed for 0-hour to 24 hours nd the total for the duration of illness. Breastmilk intake will e measured by test weighing; a computerised high precision alance will be used for this purpose. The measurement of breast ilk intake will be corrected for insensible losses that occur etween the pre-feeding and post-feeding weights (average 0.05 /kg/minute, Brown's data). Body weight will be taken by weighing hildren with diaper; diaper weight will be subtracted to get the ctual weight. For metabolic analysis, aliquot samples of food, rine and stool will be collected in addition to intake and utput measurement. Breastmilk composition will be measured by ump expresion of milk.

ata collection and analysis

The data forms will be entered into a microcomputer using a ata entry template. The pre-intervention data will be summarised nd compared among the groups. The study group will be compared ith the control group 1 for the major response variables. ignificance tests will be carried out using standard parametric ests for quantitative outcome variables. The distribution of ata will examined for validity of such tests and if necessary ppropriate transformations will be carried out before conducting he tests. Otherwise non-parametric equivalents will be used for

mparing the two groups. Exploratory analysis will also be
rried out by comparing the study group with the control group 2
r the same outcome measurements.

efinitions:

1. Type of stool:

   liquid : watery, takes the shape of the container ;

   loose : unformed stool, takes the shape of the container ;

   semi-solid : soft stool, takes own shape ;

   formed : hard stool, takes own shape.

2. Duration of diarrhoea after admission: The time in hours from initiation of the study treatment until passage of the semi-solid or formed stool in at least two successive 8-hour periods.

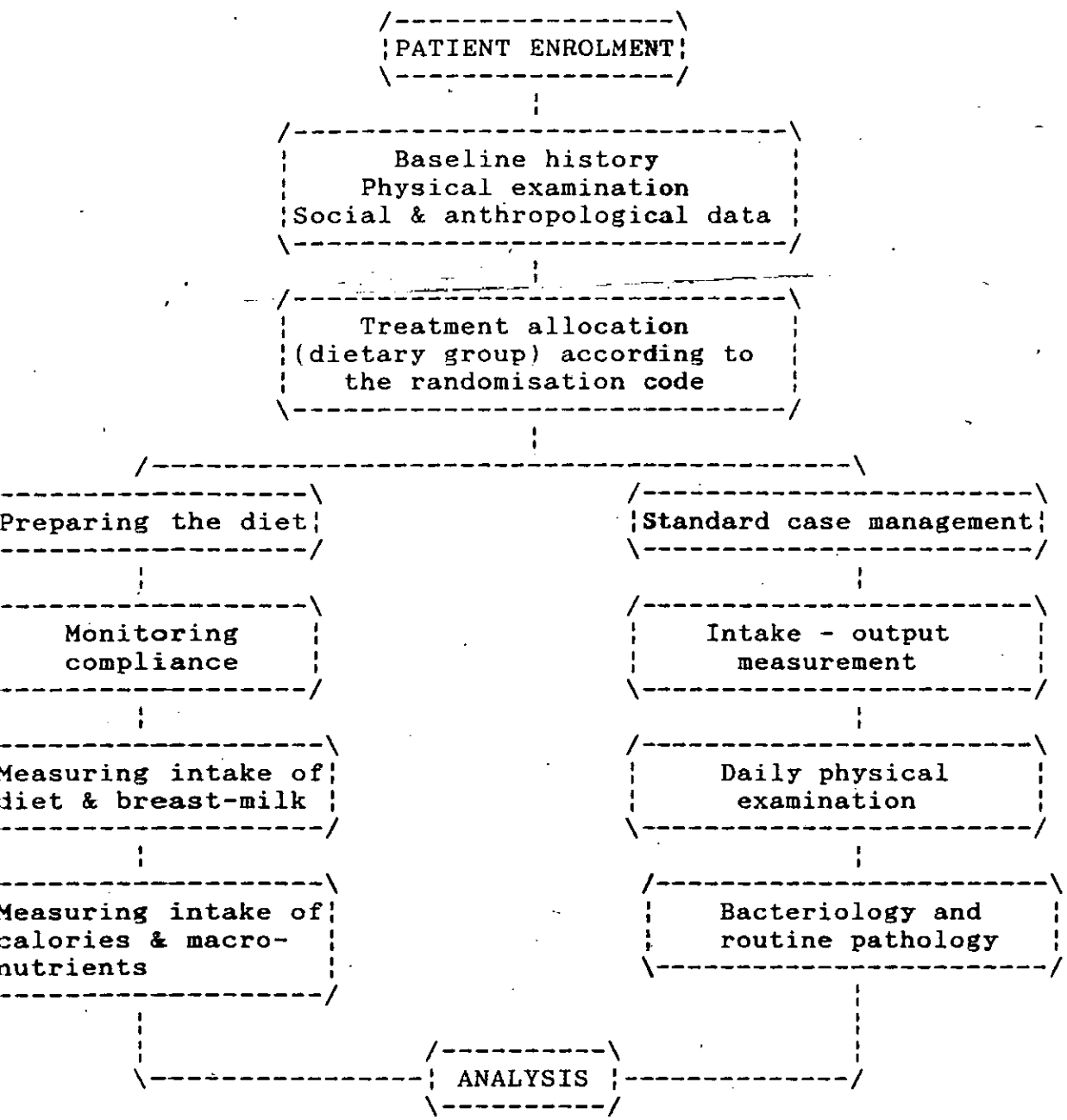
3. Stool output: The weight of stool in grams per kg of admission body weight expressed by time period e.g. per 24 hours and for the entire duration of diarrhoea.

4. Diet intake: The volume of diet taken in ml per kg of admission body weight expressed per time period e.g. per 24 hours and for the entire duration of diarrhoea.

5. ORS intake: The volume of ORS taken in ml per kg of admission body weight expressed per time period e.g. per 24 hours and for the entire duration of diarrhoea.

6. Breastmilk intake: Weight of breastmilk expressed by time period e.g. per 24 hours and for the entire duration of diarrhoea.

SEQUENCE OF TASKS



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ABSTRACT SUMMARY FOR ETHICAL REVIEW COMMITTEE

The study aims at evaluating the role of a porridge liquefied by amylase rich germinated wheat cereal flour (thereby energy dense) in increasing the calorie and nutrient intake, compared to a semi-solid porridge with the same energy density, or a porridge made liquid by adding water (thereby low energy dense), in infants and young children aged 5 months to 23 months with acute watery diarrhoea.

There is no potential risk involved.

The children will be under constant observation of the physicians, health assistants and volunteers.

During data analysis only the identification numbers of the children will be used and confidentiality will be maintained.

Written informed consent will be obtained from the authorised legal guardians or parents before the patients are included in the study.

Stool samples will be taken on admission for microscopy and culture.

Venous blood samples (2ml) will be taken on admission for TC, DC, HCT, Specific gravity, and electrolytes, repeated on the 2nd day to assess hydration. This is a routine procedure.

Standard case management of the ICDDR,B hospital will be followed in all cases.

EVALUATION OF A WEANING FOOD IN CHILDREN WITH WATERY DIARRHOEA

CONSENT FORM

Appropriate feeding is an essential component of diarrhoeal anagement. Children, in practice, fail to get or swallow enough ood that is needed for their development. The problem is orsened by anorexia during diarrhoea. Use of a liquefied energy ense porridge is likely to increase the intake and availability f calories and nutrients by the child.

We plan to add some amount of germinated wheat cereal flour ith rice or rice plus lentil to liquefy the porridge and make it nergy- and nutrient-dense. Another food will be prepared with he same ingredients but without addition of germinated wheat lour. The second food will be energy-dense but thicker. A third ood item will be made liquid by adding water to same viscosity f the first food, but lower energy density. We like to evaluate he proportion of food and nutrient intake by the children on hese three different dietary regimen.

By random selection, your baby may get any of these three ypes of food. In addition to breast milk (if breastfed), the cheduled food will be served 4 times in 24 hours. After dmission, a sample of stool and 2ml of venous blood will be ollected for the diagnosis of type and severity of illness, and

epeated on the 2nd day to assess hydration. The energy and utrient intakes will be measured from aliquotes of stool, urine nd food. The baby will be weighed daily in the morning and each me before and after breastfeeding. The baby will be provided th other treatments and medicines appropriate for his/her llness.

If you agree upon the above-mentioned conditions and allow our child to participate to this research, please sign (or left humb impression) at the bottom. Even if you do not agree, your hild must get all treatments from this hospital. You must have he right to withdraw your child anytime from the study.

.I.	Witness	Guardian

ডায়রিয়াতে একটি শক্তি ও পুষ্টি সমৃদ্ধ তরল শিশু খাদ্যের ভক্ষণ পরীক্ষণ

॥ স্বীকৃতি পত্র ॥

ডায়রিয়া চিকিৎসায় সঠিক খাবারের ব্যবস্থা করা অত্যন্ত প্রয়োজন। প্রকৃত পক্ষে শিশুর দৈহিক বৃদ্ধির জন্য প্রতিদিন যে খাবারের প্রয়োজন, শিশু তা পরিমান মতো খেতে পারে না। তদুপরি ডায়রিয়াতে খাবারের অরুচি আর একটি প্রধান বাঁধা। যদি কোনভাবে খাবারকে শক্তি ও পুষ্টি সমৃদ্ধ করা যায় এবং সেই সাথে খাবারকে তরল ও রাখা যায়, তাহলে শিশু সেই খাবার বেশী পরিমান খেতে পারবে এবং বেশী শক্তি ও পুষ্টি লাভ করবে।

আমরা চাল ও ডালের কিংবা শুধু চালের সাথে কিছু পরিমান অঙ্কুরিত গমের গুঁড়ো মিশিয়ে একটি শিশুখাদ্য তৈরী করেছি যা একদিকে শক্তি ও পুষ্টি সমৃদ্ধ এবং অন্যদিকে তরল হওয়ায় শিশুর খাবারের জন্য উপযোগী। পাশাপাশি শক্তি ও পুষ্টিতে প্রথম খাবারের সমান কিন্তু অপেক্ষাকৃত ঘন একটি খাবার, এবং আর একটি খাবার প্রথম খাবারের সমান তরল কিন্তু পুষ্টিমানে কম থাকবে। আমরা এই তিন ধরনের খাবারের তুলনামূলক ভক্ষণ পরীক্ষা করবো।

যাদৃচ্ছিক ভাবে আপনার শিশু এই তিন রকম খাবারের যে কোন একটি খাবার পাবে। বুকের দুধ খাবার পাশাপাশি এই খাবারটি প্রতিদিন চার বার দেয়া হবে। রোগ নির্ণয়ের জন্য শিশুর মল ও ২ মি.মি. রক্ত নিয়ে ভর্তির সময় একবার এবং দ্বিতীয় দিন আর একবার পরীক্ষা করা হবে। এছাড়া শিশু কেমন পুষ্টি লাভ করছে তা জানার জন্য প্রতিদিন শিশুর মল, মূত্র ও খাবারের অংশবিশেষ পরীক্ষা করা হবে। প্রতিদিন সকালে একবার এবং বুকের দুধ খাবার আগে ও পরে প্রতিবার শিশুর ওজন মাপা হবে। হাসপাতালে থাকাকালে শিশুর অসুখের জন্য অন্যান্য চিকিৎসা ও প্রয়োজনীয় ওষুধ দেয়া হবে।

আপনি যদি এ গবেষণায় আপনার শিশুকে অংশগ্রহণ করাতে চান, তাহলে নীচে সই (বা টিপসই) দিন। এই গবেষনায় অংশ না নিলেও আপনার শিশু এই হাসপাতালের সকল চিকিৎসা পাবে। আর একবার অংশ নেবার পরও যে কোন সময় ইচ্ছা করলে আপনি আপনার শিশুকে গবেষণা থেকে সরিয়ে নেবার অধিকার রাখবেন।

প্রধান গবেষকের স্বাক্ষর	স্বাক্ষী	অভিভাবকের স্বাক্ষর

তারিখ _____

SECTION III - BUDGET

Detailed budget			1st year	2nd year
A/C code	Personnel	% time	US$	US$
3121	Sr. Medical Officer	25%	2130	2130
	Medical Officer	25%	1690	1690
	Dietitian	100%	4225	4225
	Data Manager	25%	600	600
	Secretary	10%	620	620
3200	Paediatrician	25%	6000	6000
4600	Trainee Research Fellow (Doctor) (1)	100%	2250	2250
	Trainee Research Assistant (3)	100%	4000	4000
	Volunteer (4)	100%	2250	2250
	Trainee Lab. Research Fellow (1)	100%	1500	1500
	Data management & statistics Trainee Fellow (1)	25%	375	375
			25640	25640

Supplies & materials

3702	Glassware	50
3703	Hospital supplies	100
3704	Office supplies	100
3705	Chemical & media	100
3706	Uniform	50
3708	Laboratory supplies	100
3709	House keeping supplies	50
3714	Precision balance for measuring stool (one unit)	500
3715	Urine collection bag (1000)	2000
	Polythene sheets	500
	Rice 50 kg	1000
	Wheat 20 kg	
	Kimwipes	
	Ordinary clothes	
	Stationaries	
3716	Transportation	100
		4650

ther contractual

300	Repair & maintenance	100
300	Print & publication	500
500	Service charges	100
		700

ntdpt. Services

307 Pathological tests

Stool M/E (140 tests)	280
TC, DC (140 tests)	420
Hct, sp. gravity (140x2 tests)	850
	1550

308 Microbiological test

Stool culture (V. cholerae, ETEC, shigella) (140 tests)	1400
Stool for rotavirus (140 tests)	1400
LT & ST (50 tests)	500
	3300

4809	Bio-chemistry test		
	Stool sugar (140x3 tests)		840
	Stool osmolality (140x3 tests)		1260
	Stool electrolytes (140x3 tests)		2100
	Serum electrolytes (140 tests)		950
			5150
4810	X-ray		50
4827	Biochemistry & Nutr		
	Amylase	1.6x50	80
	Osmolality	3.0x400	1200
	Calorimetry	9.6x400	3840
	Viscosity	1.5x140	210
	Nitrogen	11.5x100	1150
	Fat	10.0x100	1000
	TLC	2.2x100	220
			7700
4813	Patient Hospitalisation 30x5x140		21000
4801	Computer charges		100
4802	Land transport- Dhaka		500
4806	Xerox & mimeograph		500
4815	Medical illustration		200
4817	Telex & communication		800
4821	Library service		50
4822	Staff clinic-Dhaka		200
			41,100
9300	Capital expenditure		
	Data management (software & hardware)		1500
	High precision balance for test weighing (one unit)		4000
			5500

Summary	1st year	2nd year
Personnel	25,640	25,640
Supplies & materials	4,650	
Other contractuals	700	
Inter-departmental services	41,100	
Capital expenditure	5,500	
Total	77,590	25,640
Overhead 30%	23,277	7,692
Grand total	100,867	33,332

Annex-1

ARF IN WATERY DIARRHOEA

BASELINE HISTORY AND EXAMINATION

atient's name:_____ Father's name:_____

ex: male=1 female=2 /__/ Age (mo): /__/__/

osp. no: /__/__/__/__/__/__/ Study no: /__/__/__/

ate adm. /__/__/__/__/__/__/ Time: /__/__/__/__/

ate study /__/__/__/__/__/__/ Time: /__/__/__/__/

uration of diarrhoea (h): /__/__/

requency of stool in last 24 h: /__/__/

tool type: watery or liquid=1
loose(semiliquid)=2 soft=3 /__/

requency of vomiting in last 24 h: /__/__/

ever: mild=1 moderate=2 high=3 stopped=4 none=5 /__/

bdominal discomfort: no=1 yes=2 unknown=9 /__/

norexia: no=1 yes=2 unknown=9 /__/

me (h) of last urine: /__/__/

ehydration: none=1 mild=2 moderate=3 severe=4 /__/

EEDING HISTORY:

reastfed: yes=1 negligible=2 never=3 stopped=4 /__/

stopped, age (mo): NA=88 /__/__/

breastfed, how frequent (approximately): /__/__/

it enough for the baby ? no=1 yes=2 NA=8 /__/

you give any supplement ? no=1 yes=2 NA=8 /__/

yes, what ? (give tick if yes, leave blank if no, NA=8, known=9)

Infant formula /__/ Cow's milk /__/ Rice powder /__/

Suzi /__/ Khichuri /__/ Biscuit /__/ Banana /__/

Family diet /__/ Not specific /__/

w frequent (no/day) do you give supplement ? __ to __

munization : none=1 partial=2 complete=3 /__/

st records of illness (within 2 mo): give tick if yes, leave ank if no, unknown=9

Diarrhoea /__/ Dysentery /__/ Pneumonia /__/

Measles /__/ Otitis /__/ Other (specify)_____

eatment before admission: /__/

none=1 antibiotic=2 specify_____

not antibiotic=3 specify_____

unknown medicine=4 not known=9

S (pk): /__/__/ Home-made saline (L): _____ IV (L): _____

thropometry:

dy weight (kg): /__/__/./__/__/ Length (cm): /__/__/./__/

bial length (cm): /__/__/./__/ MAC (cm): /__/__/./__/

iceps skin thickness (mm): /__/__/./__/

Annex-2

COMPOSITION OF DIETS*
(per 100 ml)

: FOR YOUNGER CHILDREN (aged 13 mo - 23 mo)

Ingradients	Diet 1	Diet 2	Diet 3
Rice powder	18g	20g	20g
Lentil	6g	6g	6g
Soyabean oil	3g	3g	3g
ARF	2g	-	-
Energy (kcal)	116	116	89
Common salt	0.5g	0.5g	0.5g
Water (ml)	100	100	130
PER	9.3%	9.3%	9.3%
FER	23.2%	23.2%	23.2%
CER	67.5%	67.5%	67.5%

Diet 1 = experimental diet
Diet 2 = energy dense thick porridge
Diet 3 = energy deficient liquid porridge

: FOR INFANTS (aged 6 mo - 12 mo)

Ingradients	Diet 1	Diet 2	Diet 3
Rice powder	24g	26g	26g
Soyabean oil	3g	3g	3g
ARF	2g	-	-
Energy (kcal)	116	116	89
Common salt	0.5g	0.5g	0.5g
Water (ml)	100	100	130
PER	5.2%	5.2%	5.2%
FER	24.5%	24.5%	24.5%
CER	70.3%	70.3%	70.3%

Diet 1 = experimental diet
Diet 2 = energy dense thick porridge
Diet 3 = energy deficient liquid porridge

* Compositions are calculated as proximate values from "Nutritive value of Indian foods" by Gopalan *et al.*

EPARATION OF ARF (From wheat):

. The cleaned grains of wheat are steeped in excess water (about double volume) in a stainless steel tray for 12 h.

. After 12 hours the wheat grains are drained of water.

. The steeped grains are then wrapped in moist black clean piece of cotton cloth and germinated for 48 hours at room temperature (~28°C).

4. The germinated wheat grains are spread on filter paper to remove surface moisture and dried for 12 hours under a ceiling fan in a stainless steel tray until dry to the touch. The well germinated wheat grains are then seperated from the non-germinated grains manually.

5. The dried grains are again dried in an oven at 50°C for 12 hours.

6. The oven-dried grains with shoots are ground to a fine powder in a laboratory blender. The flour is seived through a local seive (called 'chaluni'). This germinated wheat flour constitutes the ARF.

7. The ARF is stored in polythene bags.

REPARATION OF RICE GRUEL

1. Rice powder will be used for the preparation of the porridge.
2. Boiling the measured amount of rice powder or rice powder plus lentil with oil for 20-25 minutes.
3. Stiring the gruel at the later part of boiling with a local wooden stirer (called "ghutuni").
4. Remeasuring the gruel after boiling to get the desired amount.
5. Measuring the amount of ARF.
6. Mixing the ARF with the rice gruel and continuously stiring until the gruel liquifies.
7. The porridge is ready for consumption.

RECENT PUBLICATIONS OF AMAL K. MITRA

A. Publications:

1. Mitra AK, Rabbani GH. A Double-blind Controlled Trial of Bioflorin (Streptococcus faecium SF68) in Adults with Diarrhoea due to Vibrio cholerae and Enterotoxigenic Escherichia coli Gastroenterology 1990;99:220-223.

2. Mitra AK, Engleberg NC, Glass RI, Chowdhury MK. Fatal Dysentery in Rural Bangladesh J Diarrhoeal Dis Res 1990;8(1&2):12-17.

3. Mitra AK, Khan MR, Alam AN. A case of Meningococcaemia with Waterhouse-Friderichsen Syndrome in Bangladesh. Bangladesh J Child Health 1989;13(2-4):136-9.

4. Mitra AK, Kabir I and Hossain MA. Pivmecillinam-resistant *Shigella dysenteriae* type 1 infection in Bangladesh Lancet 1990;335:1461-2.

5. Mitra AK. Shigellosis: A Continuing Health Problem in Bangladesh (In press, Bangladesh Private Medical Practitioners J).

6. Baqui AH, Zaman K, Yunus M, Mitra AK, Hossain KMB, Banu H. Epidemiological and Clinical Characteristics of Shigellosis in Rural Bangladesh. J Diarrhoeal Dis Res 1988;6(1):21-28.

7. Siddique AK, Islam Q, Akram K, Mazumder Y, Mitra A, Eusof A. Cholera epidemic and natural disasters; where is the link. Trop Geogr Med 1989;41:377-82.

8. Baqui AH, Yunus M, Zaman K, Mitra AK, Hossain KMB. Surveillance of Patients Attending a Rural Diarrhoeal Treatment Centre in Bangladesh (manuscript).

9. Mitra AK, Khan MR and Alam AN. Clinical presentation and outcome of patients admitted into the intensive care unit of a diarrhoeal disease hospital (manuscript).

B. Published Abstracts:

1. Engleberg NC, Mitra AK, Haque E et al. Dysentery-related Deaths in Rural Bangladesh. In: Proceedings of Second Asian Conference on Diarrhoeal Diseases, Calcutta, 21-24 February, 1983.

2. Mitra AK, Clemens J. Risk Factors of Dysentery Deaths in Rural Areas of Matlab, Bangladesh. In: Proceedings of Third Asian Conference on Diarrhoeal Diseases, Bangkok, Thailand, 10-14 June, 1985.

3. Bennish ML, Kay BA, Wierzba T, Mitra AK, Baker SL. Comparison of Methods for Recovery of Shigella spp During Field Studies. In: Proceedings of IXth International Congress of Infectious and Parasitic Diseases, Munich, 20-26 July, 1986.

4. Mitra AK. An Approach to Protect Workers' Health. In: Rahman AJM, ed. Proceedings of Third Workshop & Training Programme on Worker's Health, Dhaka, 6-10 July, 1987: 13-5.

5. Mitra AK, Rabbani GH. A Randomized Double-blind Controlled Trial of Bioflorin (Streptococcus faecium SF68) versus Placebo in Cholera and E. coli Diarrhoea in Adults. In: Proceedings of Fifth Asian Conference on Diarrhoeal Disease, Kathmandu,Nepal, 21-23,1989.

C. On-going Protocols:

1. **Principal Investigator:**

Evaluation of the Beneficial Effects of Supplementation with Zinc and Iron on Growth and Morbidity of Infants and Children in a Poor Peri-urban Village Community: a Double-blind Randomized Trial.

2. **Co-investigator:**

Evaluation of Hyperimmune Bovine Colostrum in the Treatment of (a) Rotavirus Diarrhoea in Infants and (b) Shigella Disease in Children.

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For Mitra

MEMORANDUM

To : Dr. D. Mahalanabis
Associate Director, CSD

Date: September 02, 1990

From : Dr. M. A. Salam
Clinical Research Centre

Subject : **Review of the research protocol entitled, " Controlled trial of an energy dense porridge of rice or rice plus lentil, liquefied with added amylase rich germinated wheat cereal flour, in children aged 5 months to 23 months with acute watery diarrhoea**

Thank you for asking me to review the above mentioned protocol. Every section of the protocol is well written with clearly defined objectives and methods of procedures. I have therefore a very few comments/quarries:

1. Anonymity of the Investigators, I believe, is a standard retirement when sent for external review. Before this protocol is sent for external review, Dr. Mitra's C.V. should be parted.

2. Personnel cost (Budget section) did not consider salary increments.

3. **Response variables:** Secondary response variables to be looked at, have been mentioned. However, how those would be evaluated and analyzed have not been mentioned. What would be expected theoretical weight gain in study group considering same volume intake in say for example group 1 and 3, and is that expected to be significant with the study sample size.

4. **Sample size:** While there is no information provided on expected breast-milk intake and period of diarrhoea with diet no.1 and diet no.3, how the difference can be used in calculating sample size. I think, second para under this section adequately deals with sample size calculation.

5. **sample size for metabolic balance part:** It has been mentioned that after enrollment of 60 patients sample size will be reviewed and adjustments if required done. I wonder if that would be valid? If a difference is found and sample size determined to make that difference significant, should that be a valid procedure? Or, if I have misunderstood what has actually been meant.

6. **Allocation to treatment group(P-11)**: What is meant by patients irrevocably entered into the study. What would be period before enrollment into the study. I thought patients will be recruited based on the admission criteria for the study. What would specifically be looked for between these periods?

7. **Separate randomization for two age groups**: Within the diet groups, should the age groups be equally divided? How data of these two groups will be analyzed- separately or combined, when comparing with other diet groups? If separately analyzed, should not that affect sample size? If any effect of adding lentil in diet on intake is expected?

8. **Recording of time to breast-feeding**: This has been mentioned, will be measured accurately. How much accuracy is required and that would be achievable. This may pose a problem especially during the nights.

9. **Diet ration**: There is still some confusion in understanding if the patients will receive study diets ad lib, or a specified amount(unlikely). What will be the reason for prescribing rice-lentil diet at discharge which is under investigation? What is iso-caloric milk mixture, and how an intake of 500 ml in 24 hours can be ensured? Also, why should the amount be fixed rather than the children allowed to take ad lib?

10. **Lab. procedures**: Measuring specific gravity on study day-2 will be done to assess hydtation. What about subsequent study days? This may be important as weight gain with-in a period of only 5 days has been mentioned will be a response variable.

11. **Definitions**: Definitions for liquid, loose, semi-solid and formed stool should be provided. It appears from the definition of duration of diarrhoea that each stool passed after admission will be required to be classified. Would it be possible to do that consistently- especially during the night hours?

    Should not rehydrated weight be used in the calculation of volume intake/unit of body weight. This may be important, as dehydration status would be variable. The same question I would like to ask about expression of ORS intake.

12. **Coding forms**: Should be reviewed again. I could notice that for some variables coding have not been done, and for some additional columns will be required. If a patient takes more than one supplemented food, how that would be coded(with present code form)?. How long back of past illness will be important for this study? How to code if there are is history of more than one symptoms?

I would be happy if the Investigators find the comments useful for this well written protocol. I wish approval of this protocol by the Research Review and Ethical Review Committees.

Thank you.

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MEMORANDUM

To : Dr. D. Mahalanabis Sept 10, 1990

From : Dr.R.N.Mazumder

Subject : Review of the project proposal " Control trial of an energy dense porridge of rice or rice plus lentil, liquified with added amylase rich germinated wheat cereal flour, in children aged 5 months to 23 months with acute watery diarrhoea".

Thank you very much for the opportunity of reviewing this research proposal entitled " Control trial of an energy dense porridge of rice or rice plus lentil, liquied with added amylase rich germinated wheat cereal flour, in children aged 5 months to 23 months". It will be appreciated if the following points are taken into the consideration:

1.P 2: Abstract summary

How many patients will be studied ? In upper portion of the paragraph it is mentioned that 99 patients will be studied but later in the same paragraph it is mentioned as 100. Again only male patients will be studied or both male and female will be included in study ?.
How long they will remain in hospital ?

2.P 4: Last paragraph

Advantages of amylase should be clearly written. How amylase rich porridge would be better in absorbtion, since absorbtion of all sugars follows more less same enterocyte pathway.

3.P 6: Response variables

How long a patient will be considered having diarrhoea i.e,improvement ?
What is the unit of measurement of stool ml or kg ?

4.P 7: Metabolic balance

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What is the prebalance period, it is mentioned that 24 hours after starting diet balnce will be started but if balance of ? 3 days) 72 hours is done prebalance period should be 72 hours for stabilization.

Conclusion: This is very useful to know how simply more energy could be offered during weaning and disease period. In my opinion this protocol should pass for the approval of ERC/RRC.

Thanks.

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To : Associate Director, CSD

From : Dr N.H. Alam Date: 17/9/90

Subject : Review of the protocol entitled, "Controlled trial of an energy dense porridge of rice or rice plus lentil, liquified with added amylase rich germinated wheat cereal flour, in children aged 5 months to 23 months with acute watery diarrhoea.

Thank you very much for giving me the opportunity to review the above mentioned protocol. This is a very interesting protocol. I would like to mention the following points.

1. Inclusion criteria: The investigators intended to exclude the severely malnourished patients (i.e. gross marasmus, marasmic kwashiorkor and kwashiorkor) as subjects in the present study protocol. A sizable number of marasmus and marasmic kwashiorkor patients attend the CRC, ICDDR,B. Since the experimental diet is calorie dense and assumed to be efficiently absorbable, so, at least marasmus and marasmic kwashiorkor patients can be included in the present study and they can be analysed as subgroups.

2. Case management: In the proposed study protocol, ORS will be used for rehydration and maintenance of hydration of the patients. A question arises here, whether, ORS will interfere with food intake, particularly in high purging patients?

Previously, in such types of studies at ICDDR,B, I.V. fluid was sued for rehydration and maintenance of hydration.

If some patients get I.V. fluid in the maintenance phase due to failure of oral hydration.. Then, how should they be categorized - should they be considered as dietary failures or be excluded form the study?

Thank you.

Project Title: Controlled trial of an energy dense porridge of rice or rice plus lentil, liquified with added amylase rich germinated wheat cereal flour, in children aged 5 months to 23 moths with acute watery diarrhoea

Reviewer 1

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project	✓		
Adequacy of Project Design	✓		
Suitability of Methodology	✓		
Feasibility within time period	✓		
Appropriateness of budget		✓	
Potential value of field of knowledge	✓		

CONCLUSIONS

I support the application:

a) without qualification ☑ but please see constructive critique

b) with qualification

- on technical grounds ☐
- on level of financial support ☐

I do not support the application ☐

Protocol Controlled trial of energy dense porridge ... in children aged 5 months – 23 months with acute watery diarrhoea

Comments The pair of protocols "with acute dysentery" and "with acute watery diarrhoea" is similar as is appropriate for testing of some diets in different clinical presentations. Anthropometry is a main outcome when children with bloody diarrhoea are being studied; ~~metabolic balance is the raison d'etre~~ in the 'acute watery diarrhoea' protocol, and hence the concentration on male children. Protocols differ anomalously in minor details which should be made consistent between them e.g.

lower age limit : 5 months (this protocol); 6 months (dysentery)

stool collections : 6 hourly (this protocol); 8 hourly (dysentery)

randomization : age-stratified (this protocol); unstratified (dysentery)

ORS measurement : Yes (this protocol), No (dysentery)

additions for 'deviated cause' : 15 patients in both protocols, being one fifth (this protocol), or sixth (dysentery, despite longer hospitalization and hence more opportunity to 'deviate')

isocaloric milk feeds : four-five feeds — these should be timed in relation to diet feeds and times specified (if possible) in protocol. Or are children given milk on demand

diet : offered 4 times for 45 minutes (this protocol) but for 1 hour (dysentery)

Interim analysis : is this to be made after 60 males or after 60 enrolled children. If the former, then randomization strata should perhaps be :- (to ensure balanced allocation for metabolic bed studies in males)

	FEMALES	MALES	
(birthday pill!)	5 – 12 mths	5 – 12 mths	Requires good estimate of % admissions in your area, eg.
	13 – 23 mths	13 – 23 mths	

Body weight weighing with diaper on & then weighing diapers seems a bit of a performance; and what happens if child performs between the 2 weighings? Depends whether weights of child or of stool are the more important. The described procedure is appropriate to ensure no stool losses but may lead to inaccurate baby weights. Its alternative, as I have written it, risks inaccurate stool output records, and may therefore be the inferior option. However, protocol should include investigators' reasoning!

Breastmilk composition it seems a pity to do elaborate a metabolic bed study & rely on historical data for breastmilk composition. Composition of breastmilk of mums whose infants have diarrhoea may differ systematically from average Bangladeshi mother's breastmilk. Also composition may vary with lactation time?

Forms Dilip shows unaccustomed tolerance of UK (unknown to us in United Kingdom)

What does question "Is it sufficient?" under feeding history mean?

What should mum answer if she uses spoon & bottle i.e. both at different times?

Past record of illness (and elsewhere): avoid codes 0 = No 1 = Yes; use codes 1 = No; 2 = yes & avoid confusion between missing and No.

Preparation of rice gruel Still there is ambiguity in "measured amount of rice or rice plus lentil with oil" Detailed quantities?

Other comments As for previous protocol

Review of ICDDR,B proposal entitled, "Controlled Trial of an Energy Dense Porridge of Rice or Rice Plus Lentil, Liquified with Added Amylase Rich Germinated Wheat Cereal Flour, in Children Aged 5 Months to 23 Months with Acute Watery Diarrhoea"

P.I.: Dr. Dilip Mahalanabis

Reviewer 2

General Comments

This proposal describes a randomized clinical trial of at least six different dietary formulations for the management of children between five and 23 months of age with acute watery diarrhea. The research plan is well-described and the important topic that will be addressed requires careful scientific consideration. Therefore, I would encourage the investigators to pursue this area of research, but I would suggest certain modifications in the research plan, as follows:

1. The age range of children to be admitted to the study seems excessively large. Many children at the younger end of this age range in Bangladesh will not yet have experience with solid foods. Moreover, the amount of additional energy required by these children is quite limited. By contrast, children at the upper end of the age range may have extensive experience with solid foods and may have already discontinued breastfeeding. Because of this substantial variation in the expected dietary intakes of children in the proposed age range, the interpretation of results will be problematic. I would suggest that the age range be narrowed to 9-12 months or to a maximum of 9-15 months to facilitate the interpretation of results. Moreover, I would limit the study to either breastfed or non-breastfed infants in order to reduce the number of proposed dietary groups. Finally, I would include a mixed rice-lentil diet for all children rather than prepare different diets for children of different ages.

2. It will be important to measure both the viscosity and osmolality of the study diets. Ideally; these values should be measured during preliminary evaluations of the proposed diets. This will be necessary to assure that the diets are indeed feasible to prepare, acceptable to young children, and clinically and nutritionally appropriate.

3. The rice diet as currently proposed is inadequate in protein and multiple micronutrients. Although I recognize that this diet would be given in addition to breast milk, I believe that the diet itself should be nutritionally adequate. Thus, the relationship of micronutrients to energy should meet current international recommendations. Alternatively, supplemental vitamins and minerals could be provided in addition to the diet. (It is conceivable that the inadequacy of micronutrients will reduce the children's appetite, thereby confounding the interpretation of results).

4. The proposed number of feedings per day should be stated. The mode of feeding (hand, spoon and cup, other?) should be described. Also, the person who will feed the infants should be indicated. If the mothers are to feed their own children, it will be important to observe the feeding practices, to assure that the food is actually consumed by the child and not by another member of the family. Will some provision be made to assure that the feedings are given before or after breastfeedings or will this be left to the attendant's decretion? Finally, I believe that the proposed feeding period of 45 minutes is longer than would be realistically feasible in the village setting. Therefore, I think a shorter period of time should be permitted.

5. Because the diets will be initiated after an initial period of rehydration, it is not clear why children with severe dehydration will be eliminated from study. This should be justified.

6. The metabolic balance studies will be difficult to interpret because individual children will receive different amounts of breast milk and/or study diet. Thus, I am not sure that this aspect of the study is scientifically justified.

7. Because it will be impossible to mask the identity of the study diets, it would be helpful if the clinical measurements could be completed by someone who is unaware of the children's dietary groups. For example, measurements of stool collection and anthropometric assessments could be completed by individuals who are not responsible for the clinical management of the patients.

8. It is not clear why the amount of the diets will be limited to 200 ml/kg/24 hours. Because the number of feedings has not been described, the implication of the upper limit of intake with regard to amount of food offered per meal is not certain. If four feedings are to be offered, this implies that a maximum of 50 ml/kg/meal would be given. Our own data suggest that children can consume up to 65 or 70 ml/kg/feeding under some circumstances. Thus, imposing an arbitrary upper limit on the amount of meal provided may attenuate the response of some children to the dietary manipulations. This would tend to maximize the likelihood that the denser diets are proven to be advantageous.

9. The measurement of breast milk intake should be corrected for insensible losses that occur between the pre-feeding and post-feeding weights. Data from other studies suggest that insensible losses average 0.05 g/kg/minute. In our experience, it is often difficult to capture vomitus in a preweighed container. Therefore, it would be advisable to have preweighed towels available for the collection of vomitus.

10. It does not seem appropriate to use a blender for the preparation of the study diets, because this type of equipment would not be available to mothers in their homes. I would prefer to see the diets prepared in a manner that would be realistic for future implementation in the community.

11. I have not evaluated the budget in great detail, but I have the impression that more personnel are included than absolutely essential. For example, I am not certain why three medical officers are required (senior medical officer, medical officer, pediatrician) in addition to a full-time trainee research fellow, three trainee research assistants, four volunteers and a data management and statistics trainee fellow. Moreover, it appears that clinical care costs are budgeted separately. The statistician's position at 100% for two years also seems unnecessary. If the diets are not to be blended, the cost of the blender will obviously not be necessary. Likewise, if the metabolic balance studies are eliminated or reduced in scope, some savings in laboratory costs could be realized. If the malt flour is prepared and stored properly, it should not be necessary to measure amylase levels in all diets. I do not understand the value of measuring amylase in stool contents. Five hundred dollars for medical illustrations seems excessive.

Project Title: Controlled trial of an energy dense porridge of rice or rice plus lentil, liquified with added amylase rich germinated wheat cereal flour, in children aged 5 months to 23 moths with acute watery diarrhoea

Summary of Referee's Opinions: Please see the following table to evaluate the various aspects of the proposal by checking the appropriate boxes. Your detailed comments are sought on a separate, attached page.

	Rank Score		
	High	Medium	Low
Quality of Project	✓		
Adequacy of Project Design		✓	
Suitability of Methodology		✓	
Feasibility within time period	✓		
Appropriateness of budget			
Potential value of field of knowledge	✓		

?

CONCLUSIONS

I support the application:

a) without qualification ☐

b) with qualification

- on technical grounds ☑
- on level of financial support ☐

I do not support the application ☐

Name of Referee: Kenneth S. Brown

Signature: .....

Date: 30 Sept, 1985

Position: Professor of Nutrition

Institution: University of California, Davis

INTERNATIONAL CENTRE FOR
DIARRHOEAL DISEASE
RESEARCH, BANGLADESH

Memorandum

To : Chairman, RRC/ERC

From : Dr. Amal K. Mitra 16 October 1990

Subject : Consideration of proposal entitled, " **Controlled trial of an energy dense porridge of rice or rice plus lentil, liquefied with added amylase rich germinated wheat cereal flour, in children aged 6 months to 23 months with acute watery diarrhoea**".

The above proposal has been reviewed by three internal and two external reviewers, and all of them supported this area of research. Most of their suggestions are incorporated, however justifications are made for those comments which could not be taken into consideration :

Internal Review

1. Dr. Salam's comments :

a) **Response variables:** The secondary response variable of weight gain is dropped, because the study sample size will not be adequate to measure any appreciable difference.

b) **Sample size:** Since this is a new area of research, we have no prior information regarding the quantity of calorie and nutrient intake, the total duration of diarrhoea, and impact on breast milk intake. We calculated the sample size based on our unpublished data on food intake from a single meal of similar diets to infants (data provided on page 9 & 10).

c) **Sample size for metabolic balance part:** In absence of information from any earlier studies, we have to base on an assumption, and therefore an interim analysis is proposed to re-evaluate the sample size.

d) Allocation to treatment group: Patients will be enrolled based on the eligibility criteria ; they will be rehydrated and then allocated to the treatment group. So, randomization will take place just before the patient is ready to offer feeds, i.e. after rehydration.

e) Separate randomization for two age groups: Because of the potential variation in the expected dietary intakes of children in the proposed age range, separate randomization list will be prepared for two age groups. The two groups will be analysed separately. We have considered it for sample size calculation.

Since lentil is added to all the three diets of the older children, we do not expect any effect on response variables.

f) Recording of time to breast feeding: It is not possible to record the time of breast feeding especially during the nights. Mothers will be advised to report to the volunteers the time of breast feeding.

g) Diet ration: The assigned porridge will be offered 4 times in 24 hours ad lib. At discharge, the mothers will be advised to feed their babies as usual. Isocaloric milk mixture is specified. Milk will be offered ad lib. Changes made on the protocol.

h) Lab. procedures: After initial hydration and proper maintenance therapy, it is expected that the child will not go into further severe dehydration. Any change of state of hydration will be recorded clinically. Daily collection of blood sample in these young children is probably not necessary. We will not take weight gain as a secondary response variable.

i) Definitions: Specified in the protocol.

According to WHO guideline (WHO/CDD/CMT/87.2; page 14), we like to use admission body weight in expressing measurements per unit of body weight.

j) Coding forms: Reviewed.

2. Dr. Mazumder's comments:

a) **Abstract summary**: 99 patients of either sex will be studied in the three dietary groups ; 100 male patients will be taken in the metabolic study part ; 60 of the later will be recruited from the first part of the study (details are given in page 10).

The patients will remain in the hospital for maximum 6 days (page 14).

b) **Advantages of amylase**: Our hypothesis is to see whether bulk-reducing of the porridge by addition of small amount of amylase-rich germinated wheat flour increases intake of calorie and nutrients. Such advantages of amylase are stated in page 5 .

c) **Response variables**: Duration of diarrhoea and units of measurement of stool are stated in page 20.

d)**Metabolic balance**: For acute diarrhoea; we shall consider 24 hours as prebalance period.

3. Dr Alam's comments :

a) **Inclusion criteria**: The severely malnourished patients are more prone to systemic infections (both cause and effect). They might have separate disease entity. So we did not include them in this study. A separate study may be suggested with the malnourished children.

b) **Case management**: Initial hydration will be done either by rice-ORS or IV acetate according to state of dehydration, and maintenance of hydration will be carried out with rice-ORS. Food will be offered only after initial hydration, and not during high purging.

External Review:

Comments of Reviewer 1:

a) **Lower age limit** : will be 6 months ;

b) **Stool collections** : will be done 8 hourly ;

c) **Randomization** : will be done age- and sex-stratified as suggested by the reviewer to ensure balanced allocation for metabolic studies in males ;

d) **Isocaloric milk feeds** : suggestions incorporated ;

e) **Diet** : will be offered for 30 minutes ;

f) **Interim analysis** : suggestions incorporated ;

g) **Body weight** : suggestions incorporated ;

h) **Breast milk composition** : will be measured ;

i) **Forms** : suggestions incorporated.

Comments of Reviewer 2:

a) **Age range** : The lower limit of the age range is taken as 6 month, because supplementation is started at this age. Because of variation in dietary intakes, stratified randomization is proposed for infants (6-12 mo) and young children (13-23 mo); data will be analysed separately. We avoided using lentil in infants, because mothers do not usually give lentil to infants.

b) **Viscosity and osmolality** : These will be measured and accordingly budgeted.

c) **Vitamins and minerals** : We can not give them as a routine supplementation, because we want to make the diet simpler so that it can be in future implemented in the community. However, malnourished children do get vitamin and micronutrient supplements in our hospital; we shall follow all routine treatment procedures of this hospital.

d) **Feeding** : Suggestions incorporated.

e) **Eligibility** : Patients with severe dehydration will not be excluded.

f) Metabolic study : It is equally important to see the efficiency of absorption of calories and nutrients by the children of three different treatment groups. Intakes of breast milk and study diet can be accurately measured in the metabolic study ward of ICDDR,B. Time of doctor, nurses, dietitian, research assistants and volunteers are allocated for the metabolic study and budgeted accordingly.

g)Clinical measurements : Suggestions incorporated.

h) Diet ration : Suggestions incorporated.

i) Measurement of breast milk intake : Suggestions incorporated.

j) Use of blender : It will not be used.

k) Budget : We could curtail some of the costs, but not much. The statistician's position at 100% is reduced to 25%, cost for a blender is omitted, amylase levels of diets will be done on 50 occasions (twice a month), cost for medical illustration is reduced : in total an amount of US $ 7,931 is cut short.

We have revised our protocol according to the changes suggested by the reviewers. We would much appreciate if you approve the above proposal.

Thanks.