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# Memorandum

17 November 1999

To : Dr. Tahmeed Ahmed  
Clinical Sciences Division

From: Professor V. I. Mathan  
Research Review Committee

Sub : Protocol # 99-040

This has reference to your memo of 17<sup>th</sup> November 1999 along with a modified copy of your protocol # 99-040 entitled "Home-based nutritional rehabilitation of severely malnourished children recovering from diarrhoea". The protocol is hereby **approved** upon your appropriate addressing of the observation made by the Research Review Committee in its meeting held on 15<sup>th</sup> November 1999.

Thanking you and wishing you success in running the above mentioned study.

cc: Division Director  
Clinical Sciences Division

(FACE SHEET)

## ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator: Dr. Tahmeed Ahmed  
 Application No. 99-040  
 Title of Study: Home-based Nutritional  
 Rehabilitation of Severely Malnourished  
 Children Recovering from Diarrhoea and  
 other Acute Illnesses

Trainee Investigator (if any): \_\_\_\_\_

Supporting Agency (if Non-ICDDR,B) \_\_\_\_\_

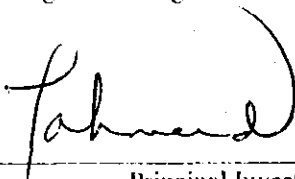
Project Status: \_\_\_\_\_

 New Study Continuation with change No change (do not fill out rest of the 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) Minor or persons under guardianship  Yes  No
2. Does the Study Involve:
- (a) Physical risk to the subjects Yes  No
- (b) Social risk 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 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 the study  Yes  No
- (b) Procedures to be followed including alternatives used  Yes  No
- (c) Physical risk NA  Yes  No
- (d) Sensitive questions NA  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 NA  Yes  No
5. Will Signed Consent Form be Required:
- (a) From subjects  Yes  No
- (b) From parents or guardian (if subjects are minor)  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 with 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. Example 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 Committee for review

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



Principal Investigator

Trainee

## RESEARCH PROTOCOL

RRC Approval: Yes/ No Date:

ERC Approval: Yes/No Date:

1. Title of Project (Do not exceed 60 characters including spaces and punctuations): **Home-based Nutritional Rehabilitation of Severely Malnourished Children Recovering from Diarrhoea and other acute illnesses.**

2a. Name of the Principal Investigator(s) (Last, Middle, First):  
**Tahmeed Ahmed**

2b. Position/Title 2c. Qualifications  
Associate Scientist MBBS, PhD

3. Name of the Division/ Branch / Programme of ICDDR, B under which the study will be carried out.  
CSD, Child Health Programme

4. Contact Address of the Principal Investigator

Clinical Sciences Division, ICDDR, B

4a. Office Address: Mohakhali, Dhaka 1212  
GPO Box 128, Dhaka  
Bangladesh

4b. Fax No: 880-2-883116/9885657

4c. E-mail: tahmeed@icddrb.org

4d. Phone: 880-2-871751-60/2304

5. Use of Human Subjects 5a. Use of Live Animal

Yes

Yes

No

No

5b. If Yes, Specify Animal Species

6. Dates of Proposed Period of Support  
(Day, Month, Year - DD/MM/YY)

1 Jan 2000 - 31 December 2001

7. Cost Required for the Budget Period

7a. 1<sup>st</sup> Year (\$): 36,089 2<sup>nd</sup> Year (\$): 38,035

7b. Direct Cost (\$): 74,124 Total Cost (\$):

### 8. Approval of the Project by the Division Director of the Applicant

The above-mentioned project has been discussed and reviewed at the Division level as well by the external reviewers.

The protocol has been revised according to the reviewer's comments and is approved.

Prof. George Fuchs, MD

Name of the Division Director



Signature


6/11/99

Date of Approval

### 9. Certification by the Principal Investigator

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

### 10. Signature of PI



Date: 4.11.99

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x Check here if appendix is included

**PROJECT SUMMARY:** Describe in concise terms, the hypothesis, objectives, and the relevant background of the project. Describe concisely the experimental design and research methods for achieving the objectives. This description will serve as a succinct and precise and accurate description of the proposed research is required. This summary must be understandable and interpretable when removed from the main application. (TYPE TEXT WITHIN THE SPACE PROVIDED).

Principal Investigator: Dr. Tahmeed Ahmed

Project Name: **Home-based Nutritional Rehabilitation of Severely Malnourished Children Recovering from Diarrhoea and other acute illnesses**

Total Budget: \$ 74,124 (direct costs)

Beginning Date: 1 JAN 2000

Ending Date: 31 DECEMBER 2001

Malnutrition is associated with more than 50% of all deaths among under-5 children. It also results in impaired development of the brain which is often irreversible unless treated at an early age. Unfortunately, nutritional rehabilitation units (NRUs) are few in Bangladesh. Moreover, hospital-based nutritional rehabilitation of severely malnourished children is expensive and any extended period of hospitalization is impractical. The proposed study will investigate the effectiveness of home-based nutritional rehabilitation compared to hospital-based management of severely malnourished children treated for diarrhoea and other associated acute illnesses at the Clinical Research and Service Centre (CRSC) of ICDDR,B. The study attempts to find an inexpensive, participatory, and sustainable alternative to expensive hospital-based nutritional rehabilitation.

Upon resolution of acute illnesses including diarrhoea, pneumonia, gross electrolyte imbalance, or septicemia, severely malnourished children aged 6 months to 5 years will be randomized to receive any of the three treatment regimens:

1. Home-based nutritional rehabilitation with home follow-up (treatment A, n=75)
2. Home-based nutritional rehabilitation with outpatient follow-up (treatment B, n=75)
3. Hospital-based nutritional rehabilitation (treatment C, n=75).

Children on treatments A and B will stay in the NRU of the CRSC for a period of 7 days, during which their condition will stabilise and their mothers will have learnt the preparation of *khichuri* and *halwa*, which are low-cost, nutritious diets being successfully used in the CRSC. Following discharge after 7 days, these children will continue to be fed *khichuri* and *halwa* prepared by the mothers at home. Children on treatment A will be visited at home for follow-up by health workers at regular intervals during which growth will be monitored, micronutrients supplied, and morbidity recorded. This will continue until the children achieve an oedema-free weight-for-height (WH) >80%. Children on treatment B will be required to attend the outpatient follow-up clinic until they achieve oedema-free WH >80%. Children on treatment C will remain in the NRU and fed *khichuri* and *halwa* according to a standardized dietary schedule until achievement of a WH >80%. Outcome measures that will be used in comparing the three treatments will include growth, time to recovery (achievement of oedema-free WH >80%), rate of weight gain in g/kg per day calculated from lowest weight to discharge weight, speed of loss of oedema, failure to respond, morbidity (number and duration of episodes over equal periods of follow-up for both groups), mortality, and cost of treatment.

KEY PERSONNEL (List names of all investigators including PI and their respective specialties)

Name	Professional Discipline/Specialty	Role in the project
1. Dr. Tahmeed Ahmed	Paediatrician & Nutritionist	P.I.
2. Dr. M.A. Salam	Internist	Co-investigator
3. Dr. G.J. Fuchs	Paediatric Gastroenterologist & Nutritionist	Co-investigator
4. Medical Officer (to be named)	Physician	Co-investigator
5. Dr. Ann Ashworth *	Nutritionist	Collaborating investigator

\* Reader in Community Nutrition  
London School of Hygiene & Tropical Medicine

Principal and co-investigators are from the Clinical Sciences Division, ICDDR,B.

## • DESCRIPTION OF THE RESEARCH PROJECT

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Concisely list in order, in the space provided, the hypothesis to be tested and the Specific Aims of the proposed study. Provide the scientific basis of the hypothesis, critically examining the observations leading to the formulation of the hypothesis.

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### **Hypothesis to be tested:**

1. After an initial period of hospitalization, severely malnourished children recovering from diarrhoea can be managed at home using indigenous, low-cost, and culturally acceptable diets.
2. The cost-benefit of a home-based programme for nutritional rehabilitation of severely malnourished children recovering from diarrhoea will be more than the conventional hospital-based programme.

### **Specific Aims:**

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Describe the specific aims of the proposed study. State the specific parameters, biological functions/ rates/ processes that will be assessed by specific methods (TYPE WITHIN LIMITS).

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1. To plan, organize and establish an effective home-based programme for rehabilitation of severely malnourished children recovering from diarrhoea.
2. To compare by means of a prospective, randomised study, the outcome, including growth, rate of weight gain, speed of loss of oedema, days to achieve oedema-free weight-for-height (WH) 80% of National Centre for Health Statistics (NCHS) median reference, failure to respond to nutritional therapy, morbidity, mortality, and cost of treatment of children managed by home-based nutritional rehabilitation (with follow-up at outpatient clinic or at home) with those managed in the conventional hospital-based programme (definition of failure to respond and morbid conditions are detailed in the *methods* section).

## Background of the Project including Preliminary Observations

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Describe the relevant background of the proposed study. Discuss the previous related works on the subject by citing specific references. Describe logically how the present hypothesis is supported by the relevant background observations including any preliminary results that may be available. Critically analyze available knowledge in the field of the proposed study and discuss the questions and gaps in the knowledge that need to be fulfilled to achieve the proposed goals. Provide scientific validity of the hypothesis on the basis of background information. If there is no sufficient information on the subject, indicate the need to develop new knowledge. Also include the **significance and rationale** of the proposed work by specifically discussing how these accomplishments will bring benefit to human health in relation to biomedical, social, and environmental perspectives. (DO NOT EXCEED 5 PAGES. USE CONTINUATION SHEETS).

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Malnutrition of under-5 children is a major health problem of the developing countries [1] and is associated with 54% of all deaths in this age group [2]. Death rates among severely malnourished children have remained almost unchanged over the last five decades, and are as high as 49% even during the 1990s [3]. This signifies inadequacies/ineffectiveness of programmes to address this issue.

About 94% of under-5 children in Bangladesh suffer from malnutrition of one kind or another, and about 66% of the children are stunted and 15% are wasted [4]. Thus, malnutrition has been correctly identified as the "silent emergency" in Bangladesh [5]. Malnutrition not only causes a short stature and reduced physical output, but when occurs early in life is often associated with impaired development of brain which is irreversible unless efficiently corrected. Thus, there is an increasing concern about the future intellectual potentials of Bangladesh.

The current management and/or rehabilitation of severely malnourished children is heavily dependent on expensive hospital- or nutritional rehabilitation unit (NRU)-based care where, most often, children are brought for other acute medical problems. There are only a few nutritional rehabilitation units in the city of Dhaka which is populated by nearly 10 million people- about 1/12th of the entire country, with a much fewer-than-required beds. Logically, therefore, such hospital/health care centre-based programmes are not likely to make any significant improvement of the ever pervasive problem of malnutrition in Bangladesh.

Most residential NRUs require that the mothers remain with their children, while the day care centres require that the mothers bring their children and take them home on a daily basis. Since most mothers have other family commitments including taking care of other children, while some mothers may have occupational problems, and day care strategies may require travelling a long distance often involving a substantial amount of money, such programmes fail to meet the specific requirements of the target group. Consequently, dropout rates from such programmes are also very high. This requires development of a programme which is effective, sustainable, likely to be acceptable to all mothers, and cost-effective.

For a successful nutritional rehabilitation programme it is very important to identify and effectively treat acute medical conditions that not only accompany such children but are also the principal reasons for taking them to a health-care facility. Nutritional rehabilitation involves provision of high calorie food containing adequate amounts of protein. On the other hand, in determining the optimal food for nutritional rehabilitation of severely malnourished children, it is also important that the food be inexpensive, easy to prepare, culturally acceptable to mothers and



children, and the ingredients are locally available. *Khichuri* and *halwa* (appendix 1) are examples of such diets developed for severely malnourished children at the ICDDR,B with optimum amount of ingredients, and are being used successfully in nutritional rehabilitation [6]. *Khichuri* is an energy-dense diet prepared from rice, soya oil, vegetables, and lentils while *halwa* is a more energy-dense sweet diet made from rice flour, soya oil, lentils, and molasses. Both the diets provide energy as well as protein from vegetable sources that are inexpensive and easily available.

The Clinical Research and Service Centre (CRSC) of the ICDDR,B (popularly known as the "Cholera hospital") currently treats around 115,000 patients each year and about 60% of them are under-5 children. Nearly 80% of all children (about 5,500 children) requiring treatment in the inpatient units for a longer period of time (median period of stay, 4.5 days) suffer from severe malnutrition. After recovering from diarrhoea and associated medical problems, a few of them (due to bed constraints and refusal of mothers to stay in the hospital for a longer period of time) undergo nutritional rehabilitation in the NRU run by the Child Health Programme of the CRSC. The NRU has only 16 beds where the very severely malnourished children are admitted with their mothers, treated for a period of 15-30 days, and discharged when their WH exceeds 80%, they are free of oedema, and have a good general condition. The number of beds in the NRU is clearly far less than what is required. On the other hand, a large number of mothers refuse to stay in the NRU for a long period of time because of family commitments at home. A survey done in January-May 1998 revealed that among 340 severely malnourished children eligible for admission to the NRU of the CRSC, mothers of only 142 children (42%) agreed to have their children admitted to the NRU. Children who cannot be accommodated in the NRU or those who refuse to stay for a prolonged period of time in the NRU are advised to come for follow-up at regular intervals. However, the follow-up rates have always been sub-optimal.

Community-based management of severely malnourished children has rarely been considered and tested in a methodical way [7]. However, in a study performed in Dhaka, home management of severely malnourished children after 7 days of inpatient care was found to be a cost-effective method of nutritional rehabilitation [8]. This study was done on children who were more than 12 months of age. Of 1332 children treated during the study period, 759 (57%) children were not recruited into the study because of age being less than 12 months (398), critical illness or severe anaemia (243), tuberculosis or other disease (108), or distance (10). The mean weight gain was only 4 g/kg body weight per day. Therefore, after treatment of the acute illness and an initial 7-day period of NRU care, the efficacy of defined low-cost diets including *khichuri* and *halwa* in the home management of severely malnourished younger children presenting with acute illness (with follow-up at outpatient clinic or at home) needs to be assessed. In this context, it is pertinent to mention here that in an earlier study involving the acute phase management of severely malnourished children at the ICDDR,B hospital at Dhaka, the median age of children was 6.5 months, 60% of whom had pneumonia and 30% had clinically diagnosed septicemia [9].

## Significance

The proposed study will investigate the effectiveness of home-based nutritional rehabilitation (with follow-up at outpatient clinic or at home) using indigenous, low-cost diets compared to hospital-based treatment of severely malnourished children recovering from diarrhoea and other

acute illness(es). It attempts to find an inexpensive, participatory and sustainable alternative to expensive hospital-based nutritional rehabilitation.

## Rationale

- If the hospital to home-based nutritional programme is found to be more cost-effective than the hospital-based programme, then it will be possible to rehabilitate more severely malnourished children with the same amount of available resources.
- It will be possible to extend the programme, if found to be effective, to other locations/health centres on a country-wide basis through governmental and non-governmental health care services.
- Home visits will provide health and nutrition education to the study mothers as well as neighbouring mothers, will help in the identification of medical problems and early referral of sick children to appropriate health centres.
- Active participation will help in confidence building of mothers on home management of severely malnourished children. Preparation and use of low-cost diets will help in preventing malnutrition among siblings as well as in subsequent children.

## Research Design and Methods

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Describe in detail the methods and procedures that will be used to accomplish the objectives and specific aims of the project. Discuss the alternative methods that are available and justify the use of the method proposed in the study. Justify the scientific validity of the methodological approach (biomedical, social, or environmental) as an investigation tool to achieve the specific aims. Discuss the limitations and difficulties of the proposed procedures and sufficiently justify the use of them. Discuss the ethical issues related to biomedical and social research for employing special procedures, such as invasive procedures in sick children, use of isotopes or any other hazardous materials, or social questionnaires relating to individual privacy. Point out safety procedures to be observed for protection of individuals during any situations or materials that may be injurious to human health. The methodology section should be sufficiently descriptive to allow the reviewers to make valid and unambiguous assessment of the project. (DO NOT EXCEED TEN PAGES, USE CONTINUATION SHEETS).

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### Study Design

Prospective and randomized, clinic to community study

### Enrollment Criteria

Age:	6 months to 5 years
Gender:	Either
Nutritional status:	Severely malnourished (WH < 70% of the NCHS median or with oedema)
General condition:	Resolution of acute illness including diarrhoea, pneumonia, gross electrolyte imbalance, and septicemia. Criteria of resolution of acute illnesses are outlined under <i>management of acute illness</i> .
Place of residence:	Within 10 km from the CRSC (for convenience of follow-up)

## Exclusion Criteria

- Informed consent: Failure to obtain informed consent from parents or caretakers  
Address: Children without any fixed address  
Medical conditions: Children with tuberculosis or any congenital/acquired disorder affecting growth i.e. trisomy-21 or cerebral palsy; children on an exclusion diet for the treatment of persistent diarrhoea.

## Interventions

Upon resolution of the acute illness, eligible children will be randomized to receive any of the three following interventions:

1. Home-based nutritional rehabilitation with home follow-up (treatment A, n=75)
2. Home-based nutritional rehabilitation with outpatient follow-up (treatment B, n=75)
3. Hospital-based nutritional rehabilitation (treatment C, n=75).

## Randomization

Randomization will be performed according to a random numbers table using permuted blocks of variable lengths.

## Patient Management

### Management of Acute Illness

As the children will be acutely ill with diarrhoea and other complicating illnesses including pneumonia, electrolyte imbalance, or septicemia, they will be treated in the inpatient units according to the standardized management protocol now being used in the CRSC. Implementation of this protocol resulted in a 47% reduction in mortality during the acute phase of treatment of severely malnourished children with diarrhoea admitted to the CRSC [9]. Duration of, and management provided during the acute phase of treatment will be recorded. Upon resolution of the acute illness, children will be randomized to receive any of the three interventions for nutritional rehabilitation and transferred to the NRU.

Criteria of resolution of acute illnesses are:

- Diarrhoea: No watery or liquid stools during the last 24 hours, no signs of dehydration, absence of blood or excessive mucus in stools.
- Pneumonia: No fast breathing (respiratory rate  $\leq 50$ /min in a child  $< 1$  year,  $\leq 40$ /min for a child  $\geq 1$  year of age), no chest indrawing, no wheeze, no cyanosis, able to drink, reduction in crepitations compared to admission auscultation.
- Electrolyte imbalance: Absence of lethargy or head lag, no irritability or fast breathing.

Septicemia: No signs of circulatory collapse (cold hands and feet, weak radial pulse, not alert), conscious, normal body temperature.

In addition, a child should be hungry and should not require a nasogastric tube for feeding.

### **Treatment A**

In this treatment schedule, children will stay in the NRU for 7 days during which period their clinical condition will stabilise, and their mothers or caretakers will have learnt preparation of khichuri and halwa and taking care of the children at home. Thereafter, they will be discharged and health workers will visit them at their homes at regular intervals until they achieve a WH >80%, are free of oedema, and have a good general condition. If a child develops an acute illness or the general condition is not satisfactory at the time of discharge, then the discharge will be postponed till resolution of the illness. During stay in the NRU, calories and protein are gradually increased over a period of time in a programmed way in order to achieve rapid growth involving a weight gain of more than 10 g/kg per day. A major element of the method of nutritional rehabilitation practised in the NRU of the CRSC is that the diet given to the children contains proteins derived mainly from vegetable sources. Food containing animal protein such as milk (which is given only initially), eggs, meat or fish are expensive, and the mothers of these children can hardly afford these foods when continuing nutritional rehabilitation at home.

The diet schedule to be followed for the children is as shown on the following page. This is the standardized diet schedule that is currently being routinely practiced in the NRU of the CRSC.

Diet	Item & amount	Energy intake Kcal/kg.day	Protein intake g/kg.day
1	Milk suji 10 ml/kg.feed (110ml/kg.day) 2 hrly (11 feeds per day)*	74	1.5
	Halwa 10 g/kg.feed 2 feeds per day	48	1.0
	<b>Total:</b>	<b>122</b>	<b>2.5</b>
2	Milk suji 10 ml/kg.feed (110ml/kg.day) 2 hrly (11 feeds per day)*	74	1.5
	Halwa 10 g/kg.feed 2 feeds per day	48	1.0
	Khichuri 10 g/kg.feed 2 feeds per day	29	0.6
	<b>Total:</b>	<b>151</b>	<b>3.1</b>
3	Milk suji 100 10 ml/kg.feed (110ml/kg.day) 2 hrly (11 feeds per day)*	110	2.8
	Halwa 10 g/kg.feed 2 feeds per day	48	1.0
	Khichuri 10 g/kg.feed 2 feeds per day	29	0.6
	<b>Total:</b>	<b>187</b>	<b>4.4</b>
4	Milk suji 100 10 ml/kg.feed (110ml/kg.day) 2 hrly (11 feeds per day) *	110	2.8
	Halwa 10 g/kg.feed 3 feeds per day	72	1.5
	Khichuri 10 g/kg.feed 3 feeds per day	43	0.9
	<b>Total:</b>	<b>225</b>	<b>5.2</b>
5	Milk suji 100 10 ml/kg.feed (40ml/kg.day) 6 hrly (4 feeds per day)	40	1.0
	Halwa 20 g/kg.feed 3 feeds per day	144	3.0
	Khichuri 20 g/kg.feed 3 feeds per day	87	1.8
	<b>Total:</b>	<b>271</b>	<b>5.8</b>

\* There is a gap in feeding at 4 a.m. Composition of milk suji and milk suji 100 (appendix 2)

Diets 1, 2, 3 and 4 will be provided on days 1, 2, 3 and 4 respectively. These diets ensure 2 hourly feeds with milk suji at least for the first 4-5 days of nutritional rehabilitation. Diet 5 is started when the child achieves an intake of 225 kcal/kg per day, which is possible by day 7. Most of the calorie and protein in diet 5 are derived from halwa and khichuri, the number of milk feeds being only four per day. The child will be given plain water in between the feeds, and breast feeding continued if applicable. The amount of each feed offered and actually taken will be recorded on a feeding chart. Upon discharge, the mother or caretaker will be advised to prepare khichuri and halwa at home and feed the child specified amounts or more for further nutritional rehabilitation. A plastic cup and a spoon will be provided to each child, but ingredients for khichuri and halwa will not be provided. A health worker will calculate the specified amounts of khichuri and halwa using a chart (appendix 3) and instruct the mother regarding the minimum number of cups of the diets to be given to the child each day.

**Micronutrient Supplementation:** If there is no xerophthalmia, vitamin A as a single dose will be given 200,000 units above 1 year of age, and 100,000 U for infants 6-12 months. If the child has xerophthalmia, the course of vitamin A will be completed. Zinc acetate syrup, multivitamin drops and folic acid will be provided by the health worker till the child achieves an oedema-free WH >80%. Elemental zinc will be given in a dose of 2 mg/kg per day. Multivitamin drops will be provided 1 ml twice daily if age > 1 year, 1/2 ml twice daily if age < 1 year. One ml of commercially available multivitamin drops contains vitamin A (as palmitate) 5,000 IU, vitamin D 1,000 IU, thiamine hydrochloride 1.6 mg, riboflavin 1 mg, pyridoxine hydrochloride 1 mg, nicotinamide 10 mg, calcium D-pantothenate 5 mg, and ascorbic acid 50 mg. Folic acid will be given 1.25 mg (one-fourth of a tablet) once daily. Potassium chloride syrup will be provided 4 mmol/kg per day three times daily for 5 days. Iron supplementation will be started from the *second week* of treatment and continued for 2 months. The dose is 3 mg of *elemental* iron/kg per day given once daily between meals (one tablet of *Folfe* contains 65 mg elemental iron). Children weighing 4-6 kg will be given one-fourth of a tablet *Folfe* once daily, those weighing >6 kg given one-half of a tablet. Since iron and zinc interfere with the absorption of each other, mothers will be instructed not to give these micronutrients at the same time.

**Training of Mothers or Caretakers:** During the 7 day stay in the NRU, mothers or caretakers will be given structured lessons on the causes and prevention of malnutrition, preparation of nutritious low-cost diets including halwa and khichuri, the need for emotional and physical stimulation of the child, home management of diarrhoea, how to recognise symptoms of common illnesses such as pneumonia and when to seek help, and counselling about birth spacing. This will enable them to continue care and proper feeding of the child after discharge from the NRU and also to prevent malnutrition in siblings and in subsequent children. They can also spread the knowledge acquired to other mothers in the community.

**Immunization:** Children who have not been immunized earlier will be given vaccines as per the Expanded Programme on Immunization guidelines.

**Anti-helminthic treatment:** Children >1 year of age will be given mebendazole, 100 mg two times daily for 3 days, if such treatment has not been provided in the last six months. This treatment will be provided after two weeks of nutritional rehabilitation.

**Follow-up:** After the child is discharged from the NRU, a health worker will visit the child every week for one month and then at fortnightly intervals until the child achieves an oedema-free WH >80%. During each visit, the child's general condition will be assessed, weight and height (or length) measured, presence or absence of oedema noted, supplies of micronutrients provided, compliance of feeding and micronutrient supplementation checked by 24 hours recall, and morbidity recorded, if any. To aid recall of morbid conditions, on each visit mothers will be given a pictorial calendar portraying a well child and children with diarrhoea, vomiting, cough, fever, eye infection, or discharging ears [10]. Mothers will be requested to record daily on the calendar whether the condition had been present or absent in the previous 24 hours. Morbidity will then be recorded on a precoded form with the help of the calendar. Diarrhoea will be defined as the passage of three or more watery or liquid stools per day. An episode will be considered new if at least two diarrhoea-free days intervene between the present and previous episodes. The health worker's identification of children with pneumonia of different grades of severity will be based upon WHO guidelines [11]. Lack of weight gain for two consecutive visits will constitute failure to respond. The health worker will refer to the CRSC any child with suspected serious illness, i.e., diarrhoea with some or severe dehydration, pneumonia, ear or throat infection, repeated episodes of fever, loss of appetite, or failure to respond to feeding. Self referral will also be encouraged and entertained at any hour of the day. The child will be evaluated and managed accordingly by any of the investigators (during day time) or the on-duty physician (at night). Readmission to the hospital and the NRU will depend upon existing CRSC guidelines. Any child readmitted to the NRU will not be re-enrolled into the study, but will maintain the pre-readmission status as a study subject. The physician will also record in the precoded form diagnosis, treatment, duration, and outcome of any severe illness including relapse of severe malnutrition or septicemia.

Upon attaining the target WH of more than 80%, the children will be advised to attend the nutritional follow-up clinic (NFU) of the CRSC at monthly intervals until they achieve a WH >90%. During the visits to the NFU, a health worker will discuss the overall condition of the child, the change in weight and the child's diet with the mother. Health and nutrition education of the mothers or caretakers will be reinforced.

### **Treatment B**

Children on treatment B will also stay in the NRU for a stabilisation period of 7 days during which their mothers or caretakers will have learnt preparation of khichuri and halwa and taking care of the children at home. Dietary therapy, micronutrient supplementation, training of mothers or caretakers, immunization, and anti-helminthic treatment will be the same as in treatment A. Thereafter, they will be discharged and advised to attend the NFU every week for one month and then at fortnightly intervals until they achieve an oedema-free WH >80%. If a child develops an acute illness or the general condition is not satisfactory at the time of discharge, then the discharge will be postponed till resolution of the illness. The protocol for follow-up will be the same as in treatment A, the difference being that the children will be

brought to the NFU by the parents. If a child fails to attend the NFU within 2 days of a specified follow-up day, a health worker will make a home visit, do the follow-up and reiterate the importance of bringing the child to the NFU for follow-up. The health worker, in course of her follow-up, will try to find out the reason(s) for defaulting. A previous study conducted at the NRU [12] to find out the cause of defaulting showed the principal reason to be the wrong perception of the parents that follow-up was not needed since the child was okay. Other reasons that came up during the previous study, and that will also be inquired during the follow-up visit by the health worker in this study, include: inability of the mother to come to the hospital alone, illness of the mother or child, distance, visit to village homestead, inability to leave other children at home alone, inability to afford the travel expenses, and death of the child.

### **Treatment C**

Children on treatment C will remain admitted in the NRU until they have achieved an oedema-free WH >80%, and have a good general condition. This will typically involve a stay in the NRU for 15-25 days. The standardized feeding schedule will be followed and micronutrient supplements provided until discharge (refer to treatment A). Training of mothers or caretakers, immunization, and anti-helminthic therapy will be the same as in treatment A, except that in this treatment schedule the mothers or caretakers will receive more educational lessons due to their longer stay in the NRU. Morbid conditions occurring during rehabilitation, including diarrhoea, pneumonia, or septicemia will be recorded in precoded forms. After being discharged from the NRU, the children in this group will be advised to attend the NFU at intervals of two weeks for one month, and then at monthly intervals until they achieve a WH >90%. The entire family will be encouraged to come for the follow-up visit during which preparation of khichuri and halwa will be demonstrated to the mothers and then served to all members. Health education of the mothers or caretakers will be reinforced. Iron supplementation will be continued for 2 months in usual doses. Intercurrent illnesses such as diarrhoea or pneumonia will be treated.

### **Sample Size**

A preliminary analysis of 51 severely malnourished children (WH <70%) who received nutritional rehabilitation in our NRU after recovering from diarrhoea showed that the weight gain was  $8.4 \pm 7.3$  g/kg.day, and the time to achieve WH >80% was  $22.5 \pm 6.2$  days. In designing a trial with three or more groups, it is suggested that pair-wise comparisons between groups of central interest be first decided upon [13]. It is assumed that the proposed method of home-based nutritional rehabilitation with outpatient follow-up will result in a relatively lesser weight gain of 4 g/kg per day, will require approximately 35 days to achieve WH >80%, and lead to a 35% reduction in cost of treatment. Sample sizes of 58, 15, and 24 children in each group (hospital and home-based) were calculated from the assumptions of weight gain, time to achieve WH >80%, and reduction in cost of treatment respectively.



The formula used for calculating sample size is:

$$\frac{2 (SD)^2}{WD^2} \times \text{factor for } \alpha, \beta$$

where, SD is the standard deviation, WD is the worthwhile difference, power of detection is 90%, and type I error is 0.05. Taking the greatest of the three calculated sample sizes and allowing for 20% dropouts (refusal to continue, unexpected migration of the family to an outlying area, or later diagnosed to have tuberculosis), a sample size of 75 children in each group has been estimated.

### **Outcome Measures**

- Time to recovery (achievement of WH 80%, oedema-free), in days
- Rate of weight gain, in g/kg per day calculated from lowest weight to discharge weight
- Speed of loss of oedema, in days
- Failure to respond
- Morbidity, in number and duration of episodes over equal periods of follow-up for both groups
- Mortality
- Cost of treatment

## Facilities Available

Describe the availability of physical facilities at the place where the study will be carried out. For clinical and laboratory-based studies, indicate the provision of hospital and other types of patient's care facilities and adequate laboratory support. Point out the laboratory facilities and major equipments that will be required for the study. For field studies, describe the field area including its size, population, and means of communications. (TYPE WITHIN THE PROVIDED SPACE).

In accordance with routine practice, the acute phase of treatment of severely malnourished subjects will take place in the general ward or the special care unit of the CRSC. The subjects will then be transferred to the NRU after the acute phase treatment is over. Existing diagnostic laboratory and radiology facilities of the Centre will be utilized.

## Data Analysis

Describe plans for data analysis. Indicate whether data will be analyzed by the investigators themselves or by other professionals. Specify what statistical softwares packages will be used and if the study is blinded, when the code will be opened. For clinical trials, indicate if interim data analysis will be required to monitor further progress of the study. (TYPE WITHIN THE PROVIDED SPACE).

Data will be analyzed using the SPSS Windows software. The Epi Info software will be used to calculate anthropometric indices. Enrollment characteristics will be compared between the three treatment groups. The outcome variables will be compared both within and between groups from enrollment to discharge. For normally distributed quantitative variables, means will be compared by ANOVA. Variables not normally distributed will be log transformed before analysis. Categorical variables will be compared by Chi-square test, multiple or logistic regression will be performed to minimise bias if required.

Results from all randomized children will be included in the analysis of the study. Data from children withdrawn because of failure to respond, TB, or voluntary dropout will be included in the analysis upto the time of withdrawal. A supplementary analysis excluding the children withdrawn may also be made.

## Clinical Economics

A complete, cost-benefit analysis from institutional as well as societal perspectives will be performed for all groups, starting from 7 days after randomization (point at which differential costs start). Cost of treatment to the CRSC will include capital and administrative costs, and expenses incurred for food, medicines, and laboratory tests. The cost of treatment to the parents will include expenses incurred for food, wage loss, transport and help needed at home during the mother's absence. This will be done in collaboration with the Health Economics Programme of ICDDR,B.

## **Ethical Assurance for Protection of Human Rights**

Describe in the space provided the justifications for conducting this research in human subjects. If the study needs observations on sick individuals, provide sufficient reasons for using them. Indicate how subject's rights are protected and if there is any benefit or risk to each subject of the study.

This study will test the hypothesis that severely malnourished children recovering from diarrhoea, after an initial stabilisation period, can be rehabilitated nutritionally at home. As new drugs will not be tested, conduction of this study in human subjects is justified. After the acute phase treatment is over, the subjects in the study groups (home-based nutritional rehabilitation with follow-up at home or at the follow-up clinic) will be kept in the NRU for 7 days for stabilisation of general condition. Discharge from the NRU at the end of 7 days stay will be postponed if the general condition of a child is not stable. This will negate any risk to the subject.

After discharge at the end of 7-days stay in the NRU, the children will be visited at home or advised to attend the follow-up clinic at regular intervals. Any child failing to attend the follow-up clinic will be visited at his/her home. During the follow-ups at home or at the clinic, health and nutrition education will be reinforced, growth monitored, micronutrients provided, and the child referred to the CRSC if found to be ill.

The parents will always have the right to withdraw their children from the study at any time. Children withdrawn from the study will be provided with the conventional treatment at the CRSC. Mothers of children in the study group will not have to stay in the NRU for a prolonged period of time, which is an advantage for the families.

## **Use of Animals**

Describe in the space provided the type and species of animal that will be used in the study. Justify with reasons the use of particular animal species in the experiment and the compliance of the animal ethical guidelines for conducting the proposed procedures.

Not applicable

## Literature Cited

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Identify all cited references to published literature in the text by number in parentheses. List all cited references sequentially as they appear in the text. For unpublished references, provide complete information in the text and do not include them in the list of Literature Cited. There is no page limit for this section, however exercise judgment in assessing the "standard" length.

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1. The state of the world's children 1994. Oxford: Oxford University Press. 1994:64-5.
2. Robinson D. The integrated management of childhood illness. *Africa Health*; September 1996: 20-1.
3. Schofield C, Ashworth A. Why have mortality rates for severe malnutrition remained so high? *Bull WHO* 1996;74:223-29.
4. Ministry of Health and Family Welfare, Government of the People's Republic of Bangladesh and Bangladesh Nutrition Council. Bangladesh country paper on nutrition. Dhaka, 1995.
5. UNICEF: The state of the world's children 1998.
6. Tahmeed Ahmed, Adhikary S, Fuchs GJ, Suskind RM. Assessment of a standardized dietary management protocol for the catch-up growth phase of nutritional rehabilitation in very severely malnourished children. ICDDR,B: Centre for Health and Population Research. Annual Report 1997, pp14-15.
7. Shah PM, Udani PM, Aphale RV. Domiciliary management of kwashiorkor in rural set up: a longitudinal study of clinical, economic and social aspects. *Indian Pediatr* 1971;8:805-13.
8. Khanum S, Ashworth A, Huttly SRA. Controlled trial of three approaches to the treatment of severe malnutrition. *Lancet* 1994;344:1728-32.
9. Tahmeed Ahmed, Ali M, Ullah M, Choudhury IA, Haque ME, Salam MA, Rabbani GH, Suskind RM, Fuchs GJ. Mortality in severely malnourished children with diarrhoea are use of a standardised management protocol. *Lancet* 1999;353:1919-22.
10. Khanum S, Ashworth A, Huttly SRA. Growth, morbidity, and mortality of children in Dhaka after treatment for severe malnutrition: a prospective study. *Am J Clin Nutr* 1998;67:940-5.
11. World Health Organization. Acute respiratory infections in children. Case management in small hospitals in developing countries. a manual for doctors and other health workers. WHO/ARI 90.5.
12. Nielsen CC, Islam MA, Thilsted SH, Ishrat F. Why do some families become defaulters in a hospital based nutrition rehabilitation follow-up programme? *Trop Geogr Med* 1992;44:346-51.
13. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. A tool box for field trials of interventions against tropical diseases. Eds: Smith PG and Morrow RH. Geneva, 1990.

## **Dissemination and Use of Findings**

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Describe explicitly the plans for disseminating the accomplished results. Describe what type of publication is anticipated: working papers, internal (institutional) publication, international publications, international conferences and agencies, workshops etc. Mention if the project is linked to the Government of Bangladesh through a training programme.

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Data being sparse in the field of home-based nutritional rehabilitation of severely malnourished children, it is anticipated that the findings of this study will be published in international, peer-reviewed journals and presented in local, regional and international conferences. The results of the study are also likely to influence the curriculum of training programmes on the management of severe malnutrition run by the GOB through its National Nutrition Programme to be launched in the year 2000.

## **Collaborative Arrangements**

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Describe briefly if this study involves any scientific, administrative, fiscal, or programmatic arrangements with other national or international organizations or individuals. Indicate the nature and extent of collaboration and include a letter of agreement between the applicant or his/her organization and the collaborating organization. (DO NOT EXCEED ONE PAGE)

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Dr. Ann Ashworth Hill, Reader in Community Nutrition, London School of Hygiene and Tropical Medicine is associated with this study as a collaborative investigator. Dr. Hill has provided substantial inputs towards the development of this protocol. Enclosed is a copy of her consent mail to be a collaborative investigator.

## Appendix 1

### Composition and Preparation of Halwa and Khichuri

#### Halwa

Ingredient	Amount	Energy (kcal)	Protein (g)
Wheat flour (atta)	200 g	682	24
Lentils (mashur dal)	100 g	343	26
Oil (soya)	100 ml	900	-
Molasses (brown sugar or gur)	125 g	479	0.5
Water	600 ml (to make a thick paste)	-	-
Total weight of halwa	1,000 g	-	-
Total energy and protein per kg	-	2,404	50.5

100 g of cooked halwa contains 240 kcal and 5 g protein.

1 cup (130 g) of cooked halwa contains 312 kcal and 6.5 g protein.

The dal is soaked for 30 minutes and then crushed. Atta is fried on a hot pan for a few minutes. The atta, crushed dal and oil are mixed with water. Gur is melted and added to the mixture to make a thick halwa.

## Khichuri

Ingredient	Amount	Energy (kcal)	Protein (g)
Rice	120 g	415	8
Lentils (mashur dal)	60 g	206	15.6
Oil (soya)	70 ml	630	-
Potato	100 g	97	1.6
Pumpkin	100 g	25	1.4
Leafy vegetable (shak)	80 g	22	2
Onion (2 medium size)	50 g	25	-
Spices *	50 g	22	1
Water	1,000 ml	-	-
Total weight of khichuri	1,000 g	-	-
Total energy and protein per kg	-	1,442	29.6

Spices include ginger, garlic, turmeric, coriander powder

100 g of cooked khichuri contains 145 kcal and 3 g protein.

1 cup (130 g) of cooked khichuri contains 190 kcal and 4 g protein.

Rice, dal, oil, spices and water are added to a pot and boiled. After about 20 minutes, the potatoes and pumpkin cut into pieces, and spices are added. Just 5 minutes before the rice is cooked, cleaned and chopped leafy vegetable is added. The pot is kept covered during cooking. Khichuri takes about 50 minutes to cook.

Halwa and khichuri can be kept in room temperature for 6 hours.

## Appendix 2

### Composition of Milk suji and Milk suji 100

Ingredients	Milk suji	Milk suji 100
Whole milk powder (g)	40	80
Rice powder (g)	40	50
Sugar (g)	25	50
Soya oil (g)	25	25
Magnesium chloride (g)	0.5	0.5
Potassium chloride (g)	1.0	1.0
Calcium lactate (g)	2.0	0.0
Cooked volume (L)	1.0	1.0
Energy (kcal/100 mL)	67	100
Protein (g/100 mL)	1.4	2.6
PER%	8	10
FER%	47	40

PER is protein-energy ratio, which indicates the amount of calories coming from protein. FER is fat-energy ratio that indicates the amount of calories derived from fat.



### Appendix 3

## Calculation of Diet Providing 200 kcal per kg per Day

1 cup khichuri = 190 kcal

1 cup halwa = 312 kcal

Weight in kg	Kcal	Number of Cups	
		Khichuri	Halwa
3	600	1	1½
3.5	700	1½	1½
4	800	1	2
4.5	900	1½	2
5	1000	2	2
5.5	1100	2½	2
6	1200	3	2
6.5	1300	3	2½
7	1400	3	3
7.5	1500	3	3
8	1600	3	3½
8.5	1700	3	3½
9	1800	3	4
9.5	1900	3½	4
10	2000	4	4
10.5	2100	4½	4
11	2200	5	4
11.5	2300	5½	4
12	2400	2400	4

## Biography of the Investigators

Give biographical data in the following table for key personnel including the Principal Investigator. Use a photocopy of this page for each investigator.

Name	Position	Date of Birth
Dr. Tahmeed Ahmed	Associate Scientist & Coordinator Child Health Programme Clinical Sciences Division ICDDR,B	24 November, 1959

**Academic Qualifications** (Begin with baccalaureate or other initial professional education)

Institution and Location	Degree	Year	Field of Study
Mymensingh Medical College, Univ of Dhaka	MBBS	1983	Medical Science
University of Tsukuba, Japan	PhD	1996	Food allergy in children

### Research and Professional Experience

1. In-service training majoring in internal medicine, from December 1983 to December 1984, at Mymensingh Medical College Hospital.
2. Medical Officer (Maternal & Child Health and Family Planning), Rural Health Complex, Ministry of Health, GoB till February 1985.
3. Joined as Medical Officer, Clinical Research Centre, ICDDR,B on 25 February 1985.
4. Worked in Dhaka Children's Hospital as a resident in Pediatrics from August 1989 to August 1990, on deputation from the Centre.
5. Clinical training in the Dept. of Pediatrics, University of Tsukuba Hospital, Japan from October 1990 to March 1992.

Concluding with the present position, list, in chronological order, previous positions held, experience, and honours. Indicate current membership on any professional societies or public committees. List, in, chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. (DO NOT EXCEED TWO PAGES, USE CONTINUATION SHEETS).

### Honours

1. Awarded the "Fellowship for innovative research in developing countries" in 1990 by the International Health Federation, UK.
2. Best paper award in Pediatric Gastroenterology in the annual conference of the Commonwealth Society for Pediatric Gastroenterology and Indian Pediatric Association, 1998.
3. International Health Research Award for 1999, Ambulatory Pediatric Association of USA.

## Bibliography

### Publications during the past three years

1. Mortality in severely malnourished children with diarrhoea and use of a standardised management protocol. Ahmed T, Ali M, Ullah M, Choudhury I, Haque E, Salam A, Rabbani G, Suskind R, Fuchs G. *Lancet* 1999;353:1919-22.
2. Humoral immune and clinical responses to food antigens following acute diarrhea in children. Ahmed T, Sumazaki R, Shibasaki M, Nagai Y, Shin K, Fuchs GJ, Takita H. *J Paediatr Child Health* 1998;34:229-232.
3. Circulating antibodies to common food antigens in Japanese children with IDDM. Ahmed T, Komota T, Sumazaki R, Shibasaki M, Hirano T, Takita H. *Diabetes Care* 1997;20:74-76.
4. Immune response to food antigens: Kinetics of food-specific antibodies in the normal population. Ahmed T, Sumazaki R, Shibasaki M, Takita H. *Acta Paediatr Japonica* 1997;39:322-328.
5. Gastrointestinal allergy to food: a review. Ahmed T and Fuchs G. *J Diarrhoeal Dis Res* 1997;15:211-223.
6. Resolution of protein-losing hypertrophic gastropathy by eradication of *Helicobacter pylori*. Yamada S, Sumazaki R, Ahmed T, Takita H. *Eur J Pediatr* 1997;156:182-185.
7. Cow's milk allergy in children: association with IgG and IgE antibodies to milk protein and presentation of a case. Ahmed T, Sumazaki R, Shibasaki M, Takita H. In: Book of programme and abstracts, Sixth Annual Scientific Conference, ICDDR,B, 1997, p58.
8. Standardised management reduces mortality among severely malnourished children with diarrhoea. Ahmed T, Ali M, Ullah M, et al. *J Diarrhoeal Dis Res* 1998;16:42.

## Detailed Budget for New Proposal

Project Title: Home-based Nutritional Rehabilitation of Severely Malnourished Children Recovering from Diarrhoea

Name of PI: Dr. Tahmeed Ahmed

Protocol Number: Name of Division: CSD

Funding Source: SDC/NCOE (World Bank) Amount Funded (direct): Total: Overhead (%) 0.5 per agreement

Starting Date: Closing Date:

Strategic Plan Priority Code(s):

Sl. No	Account Description	Salary Support			US \$ Amount Requested		
		Personnel	Position	Effort %	Salary	1st Yr	2nd Yr
1.	Dr. Tahmeed Ahmed	PI	25	NO-C	3,221	3,350	6,571
2.	Dr. M.A. Salam	Co-PI	05	NO-D	1,020	1,061	2,081
3.	Dr. George J. Fuchs	Co-PI	05		0	0	0
4.	Medical Officer – to be selected		100	NO-A	7,576	7,879	15,455
5.	Health Assistant – to be selected		100 x 4	GS-3	10,772	11,203	21,975
6.	Health Worker – to be selected		100 x 6	CSA	3,600	3,600	7,200
	<b>Sub Total</b>				<b>26,189</b>	<b>27,093</b>	<b>53,282</b>
	<b>International Travel: for presentation of study findings</b>				0	4,000	4,000
	<b>Sub Total</b>					<b>4,000</b>	<b>4,000</b>
	<b>Supplies and Materials (Description of Items)</b>						
	Medicines				1,500	1,500	3,000
	Office stationery				1,500	1,500	3,000
	<b>Sub Totals</b>				<b>3,000</b>	<b>3,000</b>	<b>6,000</b>
	<b>Other Contractual Services</b>						
	Repair and Maintenance				100	100	200
	Rent, Communications, Utilities				1,000	1,000	2,000
	Transport for home visits [120 children x 8 visits=960 visits]				1,500	1,500	3,000
	Printing and Publication				100	200	300
	<b>Sub Total</b>				<b>2,700</b>	<b>2,800</b>	<b>5,500</b>
	<b>Interdepartmental Services</b>						
	Pathological Tests				200	200	400
	Microbiological tests				200	200	400
	Biochemistry Tests				200	200	400
	X-Rays				200	200	400
	Xerox & mimeo				100	100	200
	Audiovisual support				100	100	200
	Local transport, Dhaka				200	142	342
	<b>Sub-Total:</b>				<b>1200</b>	<b>1142</b>	<b>2342</b>
	<b>Capital expenditure (Computer with accessories)</b>				3,000	0	3,000
	<b>TOTAL DIRECT COST</b>				<b>36,089</b>	<b>38,035</b>	<b>74,124</b>

187/11/99

## Budget Justifications

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Please provide one page statement justifying the budgeted amount for each major item. Justify use of manpower, major equipment, and laboratory services.

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### Manpower

- Dr. Tahmeed Ahmed: Responsible for protocol development, fund procurement, supervision of project staff, provision of care to the patients, data management and analysis. This will involve 25% of the PI's time.
- Dr. M.A. Salam: 5% of the investigator's total efforts will be directed to ensuring quality of patient care and supervision of project staff.
- Dr. George Fuchs: Helped the PI in development of the protocol. Will advise on data management, analysis, and manuscript preparation.
- Medical Officer: Responsible for enrollment and management of patients. Will also supervise project staff. Data entry, data cleaning and analysis will also be performed by the incumbent, on a 100% effort basis.
- Health Assistants: Will perform the follow-ups on children enrolled in the study. Approximately 125 children will need the home visits by the health assistants. Will also provide ancillary support to the care of children while they stay in the hospital. These works will require 100% efforts from the health assistants.
- Health Workers: Will provide ancillary support to the care of children while they stay in the hospital, and help the health assistants during follow-up visits. Given the work load at a follow-up visit and for security reasons in going out alone, a health worker will need to accompany a health assistant on a follow-up visit.

### Supplies & interdepartmental services

The children will require medicines and diagnostic tests whenever they have any inter-current illness. The budget for medicines and interdepartmental services including use of diagnostic facilities is justified in view of the high morbidity among severely malnourished children.

### Utilities and transport

Children in one of the study groups will be visited at home by health assistants and health workers. Children in another group will be visited at home if they fail to attend the follow-up clinic. These visits will involve transport fare.

### International travel

This will cover travel and per diem costs for travel abroad for dissemination of study results.

## Other Support

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Describe sources, amount, duration, and grant number of all other research funding currently granted to PI or under consideration. (DO NOT EXCEED ONE PAGE FOR EACH INVESTIGATOR)

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Not applicable

**APPENDIX 4**  
**International Centre for Diarrhoeal Disease Research, Bangladesh**  
**Voluntary Consent Form**

**Title of the Research Project: Home-based nutritional rehabilitation of severely malnourished children recovering from diarrhoea and other acute illnesses**

**Principal Investigator: Dr. Tahmeed Ahmed**

Before recruiting into the study, the study subject must be informed about the objectives, procedures, and potential benefits and risks involved in the study. Details of all procedures must be provided including their risks, utility, duration, frequencies, and severity. All questions of the subject must be answered to his/ her satisfaction, indicating that the participation is purely voluntary. For children, consents must be obtained from their parents or legal guardians. The subject must indicate his/ her acceptance of participation by signing or thumb printing on this form.

Your child is suffering from severe malnutrition which is a major cause of death in children of many developing countries including Bangladesh. Conventional treatment of your child requires that s/he stays (along with the mother or any other female caretaker) in the nutrition unit of this hospital for a period of 2-3 weeks after recovering from the acute illness(es). This long period of hospital stay has its inherent disadvantages and is, therefore, not convenient to many parents or caretakers.

We would like to investigate the usefulness of continuing nutritional management of your child at your home after keeping him/her in the nutrition unit for a period of one week only.

If you agree, your child will be transferred and kept in the nutrition unit for one week after recovery from diarrhoea or any other complicated illness. In the nutrition unit, your child will be fed milk suji, halwa and khichuri that are low-cost, easy to prepare, nutritious diets. Other medicines including vitamins and minerals will be provided. The child will be immunized against the common infectious illnesses, if not done earlier. The mother, who will also be required to stay with the child, will be provided with food and regular lessons on health and nutrition education. She will also take part in preparation of the diets for the children on a voluntary basis so that she learns the correct way of preparing the diets. In order to monitor the progress of your child, his/her height, weight, and mid-upper arm circumference will be measured on admission and discharge. You will be given advice for continuing further nutritional management and care at home until the child achieves a desirable weight.

After one week of stay in the nutrition unit, there will be three options for your child's further management until achievement of a desirable weight: discharge and follow-up at your home by our health workers at regular intervals, discharge with your subsequent attendance at our hospital's follow-up clinic, and continuation of stay in the hospital's nutrition unit for 2-3 weeks. Your child will be assigned to any of the three options by means of a process similar to a lottery, but upon which we have no control.

Participation of your child in this study is voluntary. If you do not wish to participate in the study, your child will get the standard treatment offered by this hospital. If at any stage after enrollment you wish to withdraw your child from the study, you may do so and in that case your child will get the standard treatment. All information of your child will be kept confidential. If you agree to participate your child in this study please sign on this form.

\_\_\_\_\_  
Signature of the PI

\_\_\_\_\_  
Signature/Left Thumb impression of the guardian

Date: \_\_\_\_\_

Date: \_\_\_\_\_

Witness: \_\_\_\_\_

সম্মতি পত্র

গবেষণার নাম : ডায়রিয়া ও অন্যান্য তাৎক্ষণিক রোগ থেকে মুক্তিলাভের পর তীব্র পুষ্টিহীন শিশুদের বাড়ী ভিত্তিক পুষ্টিগত পুনর্বাসন

প্রধান গবেষকের নাম : ডাঃ তাহমিদ আহমেদ

আপনার শিশু তীব্র পুষ্টিহীনতায় ভুগছে। বাংলাদেশ সহ অন্যান্য উন্নয়নশীল দেশে শিশু মৃত্যুর অন্যতম কারণ তীব্রপুষ্টিহীনতা। তীব্র পুষ্টিহীনতার সনাতন চিকিৎসা অনুযায়ী শিশুকে কোন তাৎক্ষণিক রোগ মুক্তির পর হাসপাতালের পুষ্টি ওয়ার্ডে ২-৩ সপ্তাহ থেকে চিকিৎসা নিতে হয়। এই সময় শিশুর মা অথবা অন্য কোন পরিচর্যাকারী মহিলাকে শিশুর সাথে থাকাটা অত্যাবশ্যিক। দীর্ঘদিন হাসপাতালে থাকলে অনেক অসুবিধার সৃষ্টি হয় এবং অনেক মা বাবা অথবা পরিচর্যাকারীরা তা পছন্দ করেন না।

আমরা আপনার শিশুকে পুষ্টি ওয়ার্ডে এক সপ্তাহ রাখার পর আপনার বাড়ীতে তার পুষ্টিগত পরিচর্যার কার্যকারীতা পরীক্ষা করে দেখতে চাই। আপনি সম্মত হলে আপনার শিশুকে তার ডায়রিয়া অথবা অন্যান্য তাৎক্ষণিক রোগ সেরে যাবার পর পুষ্টি ওয়ার্ডে ১ সপ্তাহ রাখবো। পুষ্টি ওয়ার্ডে শিশুকে দুধ-সুজি, হালুয়া ও খিচুরী খাওয়ানো হবে। এই খাবারগুলো সস্তা, পুষ্টিকর এবং সহজেই তৈরী করা যায়। ভিটামিন এবং অন্যান্য প্রয়োজনীয় ঔষধও শিশুকে খাওয়ানো হবে। যদি আপনার শিশুকে পূর্বে প্রচলিত ছোয়াচে রোগের প্রতিষেধক টিকা না দেয়া হয়ে থাকে, তাহলে শিশুকে সেই টিকাগুলো দেয়া হবে। শিশুর সাথে থাকাকালীন সময়ে মাকেও আহার ও স্বাস্থ্য এবং পুষ্টির উপর বিশেষ শিক্ষা দেয়া হবে। সঠিক উপায়ে পুষ্টিকর খাবার তৈরী করবার লক্ষ্যে মাকে স্বেচ্ছায় শিশুদের খাবার তৈরী করতে দেয়া হবে। শিশুর অবস্থা পর্যবেক্ষণ করার জন্য হাসপাতালে ভর্তি এবং ছুটির সময় তার উচ্চতা, ওজন এবং উর্দ্ধ বাহুর পরিধি মাপ নেয়া হবে। কাক্সিত ওজন বৃদ্ধি না হওয়া পর্যন্ত কিভাবে বাড়ীতে শিশুর খাবারের ব্যবস্থা এবং পরিচর্যা করতে হবে, সে ব্যাপারে আপনাকে উপদেশ দেয়া হবে।

পুষ্টি ওয়ার্ডে এক সপ্তাহ থাকার পর, শিশুর পরবর্তী পরিচর্যার জন্য তিনটি উপায় থাকবে: (১) পুষ্টি ওয়ার্ড হতে ছুটির পর স্বাস্থ্য কর্মীরা নির্দিষ্ট সময়ে আপনার বাড়ীতে যেয়ে শিশুর অবস্থা পর্যবেক্ষণ করে প্রয়োজনীয় ব্যবস্থা গ্রহণ করবে। (২) পুষ্টি ওয়ার্ড থেকে ছুটির পর নির্দিষ্ট তারিখগুলোতে শিশুর অবস্থা পর্যবেক্ষণের জন্য শিশুকে নিয়ে হাসপাতালের পুষ্টি বিভাগে আসতে হবে। (৩) পুষ্টি ওয়ার্ডেই ২-৩ সপ্তাহ থাকতে হবে। আপনার শিশুর জন্য উপরে উল্লেখিত তিনটির যে কোন একটি উপায় নির্ধারিত করে দেয়া হবে। লটারীর মত একটি পদ্ধতির মাধ্যমে উপায় নির্ধারণ করা হবে। এবং এই পদ্ধতির উপর আমাদের নিয়ন্ত্রণ থাকবে না।

আপনি আপনার শিশুকে স্বেচ্ছায় এই গবেষণায় অন্তর্ভুক্ত করাতে পারেন। আপনি যদি গবেষণায় অংশগ্রহণ করাতে না চান, তাহলেও আপনার শিশুকে হাসপাতালের প্রচলিত চিকিৎসা প্রদান করা হবে। গবেষণায় অন্তর্ভুক্তির পর যে কোন সময়ে আপনি আপনার শিশুকে গবেষণা থেকে প্রত্যাহার করে নিতে পারেন। সেক্ষেত্রেও শিশুকে প্রচলিত চিকিৎসা প্রদান করা হবে। আপনার শিশুর ব্যাপারে সমস্ত তথ্য গোপন রাখা হবে। আপনি যদি আপনার শিশুকে এই গবেষণায় অন্তর্ভুক্ত করাতে চান তাহলে নীচে দস্তখত করুন/টিপসহি দিন।

প্রধান গবেষকের স্বাক্ষর

অভিভাবকের স্বাক্ষর/টিপসহি

তারিখঃ

তারিখঃ

সাক্ষী :



## ABSTRACT SUMMARY FOR THE ETHICAL REVIEW COMMITTEE

### Home-based Nutritional Rehabilitation of Severely Malnourished Children Recovering from Diarrhoea and other Acute Illnesses

Principal Investigator: Dr. Tahmeed Ahmed

Malnutrition is associated with more than 50% of all deaths among under-5 children. It also results in impaired development of the brain which is often irreversible unless treated at an early age. Unfortunately, nutritional rehabilitation units (NRUs) are few in Bangladesh. Moreover, hospital-based nutritional rehabilitation of severely malnourished children is expensive and any extended period of hospitalization is impractical and not preferred by mothers or caretakers. The proposed study will investigate the effectiveness of home-based nutritional rehabilitation compared to hospital-based management of severely malnourished children treated for diarrhoea and other associated acute illnesses at the Clinical Research and Service Centre (CRSC) of ICDDR,B. The study attempts to find an inexpensive, participatory, and sustainable alternative to expensive hospital-based nutritional rehabilitation. **(Item 1: rationale for including children in the proposed study)**

Upon resolution of acute illnesses including diarrhoea, pneumonia, gross electrolyte imbalance, or septicemia, severely malnourished children aged 6 months to 5 years **(item 1: requirements for the subject population)** will be randomized to receive any of the three treatment regimens:

1. Home-based nutritional rehabilitation with home follow-up (treatment A, n=75)
2. Home-based nutritional rehabilitation with outpatient follow-up (treatment B, n=75)
3. Hospital-based nutritional rehabilitation (treatment C, n=75).

Randomization to the treatment groups will take place only after informed consent has been taken from the authorized legal guardian or parents of the subject. The contents of the consent form which is written in Bangla, will be read and explained to the guardian or parent in the presence of a witness, i.e. a nurse or another health worker not related with the study. If the guardian or parent is able to read, sufficient time will be allowed for reading and understanding the consent form. Signature of the guardian/parent will be taken only after all questions have been answered satisfactorily. If the signature cannot be given by the guardian/parent, impression of the left thumb will be taken. **(Item 5: informed consent)**

Children on treatments A and B will stay in the NRU of the CRSC for a period of 7 days, during which their condition will stabilize and their mothers will have learnt the preparation of *khichuri* and *halwa*, which are low-cost, nutritious diets being successfully used in the CRSC. Following discharge after 7 days, these children will continue to be fed *khichuri* and *halwa* prepared by the mothers at home. Children on treatment A will be visited at home for follow-up by health workers at regular intervals during which growth will be monitored, micronutrients supplied, and morbidity recorded. This will continue until the children achieve an oedema-free weight-for-height (WH) >80%. Children on treatment B will be required to attend the outpatient follow-up clinic until they achieve oedema-free WH >80%. Children on treatment C will remain in the NRU and fed *khichuri* and *halwa* according to a standardized dietary schedule until achievement of a WH >80%.

Children in groups A and B will stay in the NRU for 7 days after being treated in the hospital for any acute illness, which takes approximately 4-7 days. At the time of discharge from the NRU, they will have stayed in the hospital for a period of 12-15 days, will have recovered from any

acute illness, and have a stable general condition. If a child develops an acute illness or the general condition is not satisfactory at the time of discharge, then the discharge will be postponed till resolution of the illness. Home visits will take place at regular intervals for group A children, and also ensured for children of group B who fail to report for follow-up at the hospital. This methodology does not pose any potential physical, psychological, social or legal risk to the children (**item 2: any potential risks**)

Outcome measures that will be used in comparing the three treatments will include growth, time to recovery (achievement of oedema-free WH >80%), rate of weight gain in g/kg per day calculated from lowest weight to discharge weight, speed of loss of oedema, failure to respond, morbidity (number and duration of episodes over equal periods of follow-up for both groups), mortality, and cost of treatment.

**Item 3: Describe procedures for protecting against or minimizing potential risks and an assessment of their likely effectiveness.** Not applicable.

**Item 4: Include a description of the methods for safeguarding confidentiality of protecting anonymity.** Children enrolled into the study will have severe malnutrition along with any acute illness, and will be managed in the hospital like any other children. However, no information will be divulged to any person not involved with the study, or to any other organization.

**Item 6: If the study involves an interview, describe where and in what context the interview will take place. State approximate length of time required for the interview.** There will be no interview other than for taking the clinical history of the child on admission, and on follow-up visits for assessing the compliance of feeding and taking of micronutrients at home (length, approximately 15 minutes on each occasion). This type of interview is routinely taken even if a child is not enrolled into any study.

**Item 7: Assess the potential benefits to be gained by the individual subject as well as the benefits which may accrue to society in general as a result of the planned work. Indicate how the benefits outweigh the risks.** The individual subject, irrespective of the treatment group allocation, will get the benefit of supervised management of severe malnutrition and acute illness(es). Mothers of children of groups A and B will be spared from spending the extended period of time (approximately 2 weeks) in the hospital while their children undergo nutritional rehabilitation. If the hospital to home-based nutritional programme is found to be more cost-effective than the hospital-based programme, then it will be possible to rehabilitate more severely malnourished children with the same amount of available resources. It will be possible to extend the programme, if found to be effective, to other locations/health centres on a country-wide basis through governmental and non-governmental health care services.

**Item 8: State if the activity requires the use of records (hospital, medical, birth, death or other), organs, tissues, body fluids, or the abortus.** Hospital records will be used.

## **Home-based nutritional rehabilitation of severely malnourished children recovering from diarrhoea and other acute illnesses**

**PI: Dr. Tahmeed Ahmed**

### **Response to comments of reviewers**

#### **Reviewer 1**

Has supported the application without qualification.

Point 1: It is not practically possible to make the dietary intakes of foods such as halwa and khichuri equal in the hospital (NRU) and at home. The study would like to investigate whether the children can be fed at home for nutritional rehabilitation using a dietary regimen identical to the one advised from the NRU. Milk suji is a component of the dietary regimen for all the 3 groups of children during the acute phase and the first 7 days of nutritional rehabilitation phase. After the first 7 days, group C children (hospital-based nutritional rehabilitation) will receive a reduced amount of milk suji. There will be no restriction upon the intake of milk for children of groups A and B at home.

Point 2: We do not think that provision of food is a sustainable solution. It is not always that poverty is the root cause of malnutrition. Observations from our nutrition unit reveal that ignorance of mothers about appropriate preparation of food using inexpensive ingredients is also a major cause of malnutrition.

#### **Reviewer 2**

Has supported the application without qualification.

A more realistic budget has been prepared after receiving the reviewer's comments.

#### **Reviewer 3**

Has supported the application with qualification.

Point 1: Since exact age determination is almost impossible, anthropometric indices including weight-for-age and height-for-age will be calculated using estimated ages. SD score is useful if the subject population has a wide age range; the range being 6 months to 5 years in this study. We have kept percentage of median (ie, weight-for-height 70%) as one of the criteria for severe malnutrition in this study because this criterion, rather than SD score, is routinely used at the CRSC. However, SD scores for the 3 anthropometric indices will also be calculated.

Point 2: Definition and specific criteria for resolution of acute illnesses are outlined in the section *Management of acute illness* (page 9).

Point 3: Acuteness of an illness lasts as long as any of the features of the acute illness are present (outlined in the section *Management of acute illness*, page 9). In our previous study (ref 9), the median period of acute illness was 4.5 days (n=627 children).

Point 4: We agree with the reviewer's opinion.

Point 5: Skin fold thickness is very difficult to measure in field situations. It is not routinely practiced in the CRSC. The following instruments will be used for anthropometry:

For weight	Salter scale
For length	Length board with graduations at millimetre level
For MUAC	TALC tape

Point 6: Agree. Would help in ascertaining whether the groups are comparable or not at randomization.

Point 7: Continuous test weighing being difficult and labour-intensive, recording breast milk intake is not feasible. Since the study children will be severely malnourished and more than six months of age, they are likely to be on no or scanty breast milk.

Point 8: The recently published WHO guidelines are conceptually identical to the management guidelines in practice at the CRSC, although there are certain differences (ref 9). Micronutrients will be supplemented separately, as practiced routinely at the CRSC.

Point 9: There is no need for an end-point hemoglobin measurement.

Point 10: The food intake in group C will continue to be quantified till discharge from the NRU on achieving oedema-free weight-for-height 80%. The advice to be rendered to the mothers on discharge has been elaborated on page 12 (paragraphs 1 and 3). This will include advice regarding the approximate amounts of food to be given to the child, and education on health and nutrition.

Point 11: We agree that the fat energy ratios (FER) of halwa and khichuri are >30%. But these ratios are much less than that of F100, which is the liquid diet recommended by the WHO for use during the nutritional rehabilitation phase of younger children. The WHO guidelines do not recommend any specific solid diet, and therefore, do not mention any thing specific about the FER of solid diets to be used during nutritional rehabilitation.

As regards caloric density, the WHO guidelines recommend that the energy value of any solid diet used in nutritional rehabilitation be *at least* 1 kcal per gram. One gram of halwa and khichuri have energy values of 1.4 and 2.4 kcal respectively.

Title: Home-based Nutritional Rehabilitation of Severely Malnourished Children Recovering from Djarrhuca

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	X		
Adequacy of project design	X		
Suitability of methodology	X		
Feasibility within time period	X		
Appropriateness of budget	X		
Potential value of field of knowledge	X		

**CONCLUSIONS**

I support the application:

a) without qualification 14

b) with qualification

- on technical grounds //

- on level of financial support //

I do not support the application //

Name of Referee: Robert Suskin

Signature: [Handwritten Signature]

Date: 10-12-99

Position: Dean

Institution: Chicago Medical School

See pg 2

1

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**Detailed Comments**

Please briefly provide your opinions of this proposal, giving special attention to the originality and feasibility of the project, its potential for providing new knowledge and the justification of financial support sought; include suggestions for modifications (scientific or financial) where you feel they are justified.

(Use additional pages if necessary)

**Title:** Home-based Nutritional Rehabilitation of Severely Malnourished Children Recovering from Diarrhoea

**PI:** Dr. Tahmeed Ahmed

**Reviewer:**

This is an excellent study, which should be undertaken and funded. There are a few points, which should be addressed in the design.

1. When comparing the effectiveness of Halwa and Khichuri at home vs. nutritional rehabilitation at the ICDDR, both groups should be on the same dietary intake independent of site. If milk suji is not included in the outpatient treatment, it should not be included in the inpatient.
2. Because of the questionable availability of money and food to rehabilitate children at home, it may be worth while having 2 groups at home. One group could be provided with food and the second not provided with food at home. One would then be able to determine the effectiveness of the center providing food vs. the family providing the food on ultimate recovery.

Good luck on this very important study.

2

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Detailed Comments

Please briefly provide your opinions of this proposal, giving special attention to the originality and feasibility of the project, its potential for providing new knowledge and the justification of financial support sought; include suggestions for modifications (scientific or financial) where you feel they are justified.

(Use additional pages if necessary)

Title: Community-based nutritional rehabilitation of severely malnourished children recovering from diarrhoea

PI: Dr. Tahmeed Ahmed

Reviewer:

Aim of this study is to investigate the effectiveness of community-based nutritional rehabilitation, which should be inexpensive, participatory and suitable, compared to hospital-based management of severely malnourished children treated for diarrhea and other associated acute illnesses at the CRSC of ICDDR, B.

Malnutrition in children, particularly of infants and toddlers, is a major health problem of developing countries and this has been the worst leading cause of death in this age group in the nearly last half century. Malnutrition in this age group causes various kinds of health problems including impaired psychomotor development. Therefore, to establish an effective program for rehabilitation of severely malnourished children, especially recovering from diarrhea, which should be inexpensive and feasible.

This referee think that as authors' proposal is considerably interesting and the program is carefully designed this merit acceptance. For the benefit of the ICDDR, B, however, an appropriateness of budget needs to be justified by someone else because this referee's knowledge of economical situation in Bangladesh is limited to evaluate it.



**Title: Home-based Nutritional Rehabilitation of Severely Malnourished Children Recovering from 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 Yes
- on technical grounds / / Yes
- on level of financial support / /

I do not support the application / /

Name of Referee: Prof. H.P.S. Sachdev

Signature: *HP Sachdev*

Date: October 15, 1999.

Position: Professor

Institution: Maulana Azad Medical College, New Delhi 110 002.

## Detailed Comments

Please briefly provide your opinions of this proposal, giving special attention to the originality and feasibility of the project, its potential for providing new knowledge and the justification of financial support sought; include suggestions for modifications (scientific or financial) where you feel they are justified.

(Use additional pages if necessary)

Title: **Home-based Nutritional Rehabilitation of Severely Malnourished Children Recovering from Diarrhoea**

PI: Dr. Tahmeed Ahmed

Reviewer: Prof. H.P.S. Sachdev

The study objectives are relevant and original in the context of developing countries in which severe life threatening malnutrition is still a major problem. We need objective evidence to formulate not only the dietary guidelines but also replicable cost-effective places for nutritional interventions since supervised settings have not only inherent difficulties but are also simply not available or too costly. The authors may like to address the following issues and/or suggestions:

1. It would be preferable to define severe malnutrition by weight for height criteria in a research setting by  $<3SD$  score rather than 70%. Although exact age is not required for determining this index, other indices are also likely to be compared later. It would therefore be pertinent if the method of determination of exact age is specified and the indices adjusted to the exact day.
2. How will the resolution of each illness be defined? We need specific criteria to be outlined.
3. What is the cut-off utilized to define the acuteness of an illness?
4. This study obviously cannot be conducted in a blinded fashion, which will remain an inherent limitation.
5. The sensitivity of the instruments and the procedures for recording Anthropometry would be desirable. The authors may also consider recording skin fold thicknesses.
6. It would be desirable to record pre-randomization co-morbidities or life threatening complications like hypothermia, hypoglycemia, dyselectrolytemia, anemia, etc.
7. During hospitalized dietary interventions, will efforts be made to record breast milk and water intake?
8. The authors may like to consult the recent WHO publication (if not already done) - Management of Severe Malnutrition, 1999. If possible, it would be desirable to use micronutrient and mineral supplementation as per their recommendations.
9. Would it be possible to incorporate at end point a simple Hemoglobin measurement?
10. It is not clear if in the NRU group, the food intake will be continue to be quantified till discharge? Further, in Group A the exact advise rendered to the mothers/relatives on sending home needs to be elaborated.
11. The Fat energy ratio of the diets (Halwa and Khichri) is exceeding 30% and also the caloric density and (? Osmolality) is high. Would the authors consider revising these in view of the current recommendations (see also WHO publication).

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# Check List

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After completing the protocol, please check that the following selected items have been included.

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1. Face Sheet Included
2. Approval of the Division Director on Face Sheet
3. Certification and Signature of PI on Face Sheet, #9 and #10
4. Table on Contents
5. Project Summary
6. Literature Cited
7. Biography of Investigators
8. Ethical Assurance
9. Consent Forms
10. Detailed Budget



Comments of a research project entitled "Home-based nutritional rehabilitation of severely malnourished children recovering from diarrhoea and other acute illnesses."

01. It is an excellent study which is very relevant to the country situation.
02. The proposed research project will study the effectiveness of home-based nutritional rehabilitation using indigenous, low-cost diets compared to hospital-based treatment of severely malnourished children recovering from diarrhoea and other acute illnesses. Follow up will be at the out-patient clinic or at home.
03. There is no simple association between mortality and the severity of weight loss in the oedematous form of protein-energy malnutrition. However a study (Lancet 1975;ii:427-429) shows that the serum albumin concentration at admission is strongly associated with mortality. Therefore the presence of oedema is not enough to detect severely malnourished children with a high risk of dying.
04. The protocol therefore may be approved.

*Hajera Mahtab*  
17.1.2000

(Prof. Hajera Mahtab)  
Director, Clinical Services,  
Research and Academy  
BIRDEM



INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH BANGLADESH

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December 28, 1999

To: Prof. Mahmudur Rahman  
Chairman, Ethical Review Committee

From: Dr. Tahmeed Ahmed  
Clinical Sciences Division

Subject: **Protocol # 99-040**

In response to your comment regarding the inclusion criteria in our proposed study entitled *Home-based nutritional rehabilitation of severely malnourished children recovering from diarrhoea and other acute illnesses*, I would like to inform you about the following points for consideration.

1. Children will be admitted to the nutritional rehabilitation unit (NRU) only upon resolution of acute illness(es) including diarrhoea, pneumonia, gross electrolyte imbalance, and septicemia. Criteria of resolution of acute illnesses have been defined in the protocol (attached herewith). Therefore, during the 7 days of stay in the NRU, the two groups of study children will be free of any acute illness that might pose a risk. However, if a child develops an acute illness during stay in the NRU or if the general condition is not satisfactory at the time of discharge, then the discharge will be postponed till resolution of the illness. This pre-condition to discharge is part of the management protocol.
2. In 41 severely malnourished children with bilateral pedal oedema consecutively admitted to our NRU for management, the median period of time taken for resolution of oedema was 7 days (mean  $\pm$  SD, 7.0  $\pm$  3.7 days). Therefore, by the time (by day 7 in our proposed study) children will be discharged from the NRU, most of them will be oedema-free.
3. In the oedematous form of protein-energy malnutrition, there is no simple association between mortality and the severity of weight loss, whereas the serum albumin concentration at admission is strongly associated with mortality (1). In a retrospective multivariate analysis seeking to find out the predictive markers of death in a cohort of 1129 children in Central Africa, serum albumin concentration, and not oedema, was found to be the best predictor of subsequent risk of dying (2). It was concluded from the study results that an isolated clinical sign such as oedema is not enough to detect severely malnourished children with a high risk of dying.

4. In a conceptually identical type of study done in Dhaka, the median period of time taken for resolution of oedema by severely malnourished children managed at home was 19 days, compared to 11 days by those managed on an inpatient basis (3). Mortality, however, was the same in both the groups, 3.5%.

In consistence with the pre-condition to discharge built within the study protocol and the literature cited, we feel that discharging some children with oedema after 7 days of NRU stay will not pose an additional risk. By the time the children are discharged, the mothers/caretakers will have learnt about proper care taking, feeding and identification of the acutely ill child.

I would, therefore, request you to reconsider your decision about the inclusion criteria in our study, and allow us to enroll children with oedema who constitute one-third of all severely malnourished children admitted to the hospital (4).

Thanking you.

cc: Division Director  
Clinical Sciences Division

#### References:

1. Hay RW, Whitehead RG, Spicer CC. Serum albumin as a prognostic indicator in oedematous malnutrition. *Lancet* 1975;ii:427-429.
2. Dramaix M, Hennart P, Brasseur D, Bahwere P, Mudjene O, Tonglet R, Donnen P, Smits R. Serum albumin concentration, arm circumference, and oedema and subsequent risk of dying in children in Central Africa. *BMJ* 1993;307:710-713.
3. Khanum S, Ashworth A, Huttly SRA. Controlled trial of three approaches to the treatment of severe malnutrition. *Lancet* 1994;344:1728-32.
4. Tahmeed Ahmed, Ali M, Ullah M, Choudhury IA, Haque ME, Salam MA, Rabbani GH, Suskind RM, Fuchs GJ. Mortality in severely malnourished children with diarrhoea are use of a standardised management protocol. *Lancet* 1999;353:1919-22.

## Criteria of resolution of acute illnesses

Diarrhoea:	No watery or liquid stools during the last 24 hours, no signs of dehydration, absence of blood or excessive mucus in stools.
Pneumonia:	No fast breathing (respiratory rate $\leq 50$ /min in a child $< 1$ year, $\leq 40$ /min for a child $\geq 1$ year of age), no chest indrawing, no wheeze, no cyanosis, able to drink, reduction in crepitations compared to admission auscultation.
Electrolyte imbalance :	Absence of lethargy or head lag, no irritability or fast breathing.
Septicemia:	No signs of circulatory collapse (cold hands and feet, weak radial pulse, not alert), conscious, normal body temperature.

In addition, a child should have a good general condition, be hungry and should not require a nasogastric tube for feeding.






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# Memorandum

15 December 1999

To : Dr. Tahmeed Ahmed  
Clinical Sciences Division

From : Professor Mahmudur Rahman   
Chairman, Ethical Review Committee

Sub : Protocol # 99-040

The Ethical Review Committee met on 8<sup>th</sup> December 1999 and considered your protocol # 99-040 entitled "Home-based nutritional rehabilitation of severely malnourished children recovering from diarrhoea". After discussion in the meeting the Committee made the following comment:

- a) in view of possible risk for sending the patients with oedema to home after 7 days, such patients should be excluded for enrollment in the study.

You are therefore advised to revise the protocol incorporating the above observation of the copy and resubmit a modified copy for consideration of the Chair.

Thank you.

cc: Division Director  
Clinical Sciences Division

**Ethical Review of Research Protocol entitled, "Home based Nutritional Rehabilitation of Severely Malnourished Children, recovering from Diarrhoea and other acute illnesses".**

The study is proposed against a backdrop of a stated relationship of malnourishment with more than 50% deaths of <5 yrs. Children. Since correction of malnutrition is linked to prevention of deaths in acute illnesses in, < 05 children, the study attempts to find an inexpensive, participatory, and sustainable alternative to expensive hospital based nutritional rehabilitation.

The aim of the study is to compare by means of a prospective, randomized study :

1. Rate of weight gain
2. Speed of loss of oedema
3. Days to achieve oedema free weight for height (WH) 80% of NCHS median reference
4. Failure to respond to nutritional therapy
5. Mortality, Morbidity
6. Cost of treatment of children managed by home based nutritional rehabilitation compared to those managed in the conventional hospital based program

The sample size for each of the comparison groups is the same i.e. 75.

The stated inclusion and exclusion criteria and the methodologies stated therein do not indicate any risks to subjects as a result of this study, and there appear to be measures to ensure adequate cover and follow up of those receiving domiciliary nutritional therapy.

**The protocol therefore is recommended for consideration by the ERC for approval.**

Mahmudur Rahman  
Prof. of Epidemiology  
NIPSOM, Dhaka.