Attachment 1.

Date _____

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. A.N. Alam

Application No. 82-011(P)

Title of Study Acceptability and Digestibility of a Wheat Syrup

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 form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects — (Yes) No
   (b) Non-ill subjects — Yes (No)
   (c) Minors or persons under guardianship — (Yes) No
2. Does the study involve:
   (a) Physical risks to the subjects — Yes (No)
   (b) Social Risks — Yes (No)
   (c) Psychological risks to subjects — Yes (No)
   (d) Discomfort to subjects — Yes (No)
   (e) Invasion of privacy — Yes (No)
   (f) Disclosure of information damaging to subject or others — Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) — (Yes) No
   (b) Use of fetal tissue or abortus — Yes (No)
   (c) Use of organs or body fluids — (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study — (Yes) No
   (b) Procedures to be followed including alternatives used — (Yes) No
   (c) Physical risks — Yes (No)
   (d) Sensitive questions — Yes (No)
   (e) Benefits to be derived — (Yes) No
   (f) Right to refuse to participate or to withdraw from study — (Yes) No
   (g) Confidential handling of data — (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — Yes (No)
5. Will signed consent form be required:
   (a) From subjects — Yes No
   (b) From parent or guardian (if subjects are minors) — (Yes) No
6. Will precautions be taken to protect anonymity of subjects — (Yes) No
7. Check documents being submitted herewith to Committee:
   ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   ___ Informed consent form for subjects
   ✓ Informed consent form for parent or guardian
   ___ Procedure for maintaining confidentiality
   ___ Questionnaire or interview schedule *

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

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

A.N. Alam
Principal Investigator

Trainee

15 JUN 1998

SECTION 1 - RESEARCH PROTOCOL

1) TITLE: ACCEPTABILITY AND DIGESTIBILITY OF A WHEAT SYRUP.

2) PRINCIPAL INVESTIGATOR: Dr. Ahmed Nurul Alam

CO-INVESTIGATORS: Dr. Sultana Khanam, Dr. Ayesha Molla and Dr. M. Mujibur Rahaman

3) STARTING DATE: April, 1982

4) COMPLETION DATE: June, 1982

5) TOTAL DIRECT COST: $ 2164

6) SCIENTIFIC PROGRAM HEAD:

This protocol has been approved by the _____ Working group.

Signature of Scientific Program Head: _____

Date: _____

7) ABSTRACT SUMMARY: The acceptability and digestibility of a specially prepared wheat grain extract made into syrup will be evaluated and net absorption of carbohydrate, nitrogen, and calories derived from the product will be determined in children between 3 to 5 years of age.

8. REVIEW:

a. Research Involving Human Subjects: _____

b. Research Review Committee: _____

c. Director: _____

d. BMRC: _____

e. Controller/Administrator: _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1. Objective:

The aim of this limited study will be to ascertain the acceptability and digestibility of a nutritive syrup from wheat which could be used for early rehabilitation of recuperating malnourished children in Bangladesh.

2. Background:

Malnutrition is the biggest contributor to child mortality in developing countries. It is usually also widespread among children in the same areas where infections are rampant. The prevalence of severe and moderate forms of protein-energy- malnutrition (PEM) in Asia & Middle East ranged from 20 to 80 percent of pre-school children (Bengoa and Donoso, 1974). The mortality rate in pre-school children who were malnourished varies between 10-30%. Diarrhoea is frequently associated with malnutrition which is thought to be due to several factors: e.g. (a) decreased food intake due to anorexia or food withholding behaviour (b) loss of major nutrients with vitamins and minerals in the facees & (c) increased tissue catabolism. In Latin America, malnutrition was recognized to be either a direct or an underlying cause of

most deaths in diarrhoeic children. Mata (1978) has observed a marked negative effect of childhood infections on physical growth. In most illnesses, catabolism overshadows anabolism. Pollack and Sheldon (1970) found the total losses to be approximately 130 G of total body nitrogen, roughly equivalent to 4 kg of body mass in the usual 20 day course of typhoid fever. Marked reduction of caloric and protein intake was observed in Bangladeshi children with acute diarrhoea by Hoyle et al (1980) and Molla et al (1981). Similar reduction in food intake has been reported in Guatemalan children (Martorell and Yarbrough, 1981). During the acute stage of diarrhoea, absorption of nitrogen was affected in diarrhoeas of all aetiologies, absorption of fat and calories comparatively less in rotavirus than in ETEC and shigella whereas absorption of carbohydrate was least affected in any stage (Molla et al, 1981). Molla et al (1981) have also shown that appetite recovers in acute diarrhoeas within 4 to 7 days of illness. It has been recommended that during the early convalescence, increased dietary intake through food of high caloric density and greater frequency of feeding should be attempted to achieve additional nutritional intake to match the amount of food not eaten during the illness (Rohde, 1981). Rehabilitation of malnourished children is a long protracted and expensive undertaking. Proper nutritional rehabilitation during recovery from illness will no doubt have a marked impact on child health and nutrition. One of the principal difficulty encountered during rehabilitation of children is the bulk of the food

that has to be used for supplying the calories. A 12-month old child, for example, would have to eat about 2 kilogram of boiled rice, to satisfy his calorie and protein requirements. If vegetables are included, the volume will increase considerably. For this reason, diet offered in supplementary feeding programs ideally should have concentrated protein and calories. This may be achieved by feeding a specially formulated food. If one could augment a nutritional rehabilitation by giving high calorie food in a volume suitable for repeated administration in children, it would be possible to reduce the duration of hospitalisation during recovery. Although it is possible to increase the calorie concentration by adding fat, it is not desirable in most cases of diarrhoea as small children recovering from acute diarrhoea may not be able to utilize fat properly. In some forms of childhood diarrhoea like rotavirus diarrhoea one of its manifestation is the presence of fat globules in the stool, perhaps due to the inability of the intestine to handle fat for absorption. Even in these types of diarrhoeas, absorption of carbohydrate seem to be quite satisfactory (Molla et al 1981). A soluble carbohydrate, if available as a polyglucose rather than readymade form of sugar or glucose, should make it possible to concentrate considerable quantity of calories in a small volume of water without increasing the sweetness or solute load. If this product is not too sweet, it should be possible to administer to children at frequent intervals and provide a high level

of calories during recovery from acute infectious illness like diarrhoea. Human and animal milk products are usually not suitable as supplementary items for administration in large quantities because of associated secondary lactase deficiency invariably present in these children (Lifshitz et al, 1971).

A highly palatable and soluble carbohydrate nutritive syrup has been prepared from powdered wheat grain by using enzymes (Dahlqvist et al, 1978). This is rich in protein and free from lactose. The composition of this new product is as follows:

Composition of the syrup

Calculated on dry matter.

Carbohydrates	87%
Protein	11.5%
Fat	0.5%
Ash	1.8%

Carbohydrates in the syrup are as follows:

Glucose (Dextrose)	3%
Maltose	53%
Maltotriose	17%
Higher maltosacch	13%
Isomaltose, sucrose Fructose	2%

Energy : 3.90 Kcal/G dry wt.

The composition of the syrup(i.e. carbohydrate, protein and fat content), kindly provided by Prof. Dahlqvist, has been verified in our biochemistry laboratory.

Advantages of the syrup

1. As it is easily dissolvable in small volume of water, one can pack a lot of calories.

2. Improved recovery of nutrients from a given quantity of cereal.

3. Absence of unabsorbable cellulose or brans.

4. Absence of lactose. This is particularly important, as it could be used in patients with lactase deficiency.

5. Can also be used in preparing soft drink, breakfast cereals or other nutrient mixtures.

Preparation of the syrup

The method to be described is principally a new method for utilization of cereals. The method is based on a wet extraction of cereal grain. This kind of extraction has considerable nutritional and technological advantages over the traditional grinding. The results which will be presented here have been obtained in experiments with wheat, but also other species of cereals such as, rye, barley, rice, oats or corn etc. can be used with similar advantages.

The wheat grain was crushed and extracted with warm enzyme solutions. The enzymes present were α-amylase and protease, which broke down and solubilized the starch and proteins present. The extract obtained was

concentrated into a syrup, after that the bran residue had been revoved and washed. The products obtained were a light brown syrup with a pleasant malty smell and taste plus a small residue of washed bran.

The main components of the syrup were carbohydrates and protein. It also contained vitamins and minerals, and a very small amount of fat (0.5%) with linoleate as the dominating component.

The carbohydrate components of the syrup were essentially hydrolysis products of starch. The degree of depolymerization can be varied within wide ranges by changes in the extraction conditions, and in this way the technological properties of the syrup can be changed according to purpose.

The essential amino acid composition of the proteins in the syrup were rather similar to those of full corn wheat meal. As expected, lysine was the limiting amino acid. There seemed to be a slight loss of lysine in the sterilization process.

The water-soluble vitamins were to a large extent eluted from the bran and recovered in the syrup. Although there was some loss of thiamine during the sterilization, not less than 60% of the thiamin of the wheat bran was recovered in the syrup. Niacin, which is more heat stable, was recovered to 80%. This is a remarkable difference from the traditional grinding of cereals, while the vitamins are lost with the bran fraction.

The minerals were also to some extent eluted, but iron and zinc were so firmly bound to the bran that in spite of repeated washing of the bran less than 10% of these minerals were recovered in the syrup.

The syrup obtained has a valuable composition from nutritional point of view. If we calculate the nutrient density (i.e. the content of different nutrients per 1000 Kcal divided by the recommended content of the same nutrient per 1000 Kcal in the diet) we find that the syrup is especially rich in protein, thiamin, and niacin.

B. SPECIFIC AIMS

(1) To ascertain the acceptability and digestibility of the wheat grain syrup in Bangladeshi children.

(2) To determine the net absorption (co-efficient of absorption) of carbohydrate, protein, calories and fat in children convalescing from malnutrition.

C. METHODS OF PROCEDURE

Twelve malnourished weaned children between 3 to 5 years of age who are recovering from malnutrition in the Childrens Nutrition Unit in Dacca will be recruited forthe study. Those with systemic infections metabolic disease or on antibiotic or chemotherapy will be excluded. Informed consent will be obtained from their parents or guardians before taking part in the study. No antibiotics will be administered

to the children till the study is completed. After an overnight fast, patients will be fed 5 gms of d-xylose in 100 ml of water. 1 hr. after ingestion, 1 ml venous blood will be drawn to estimate the xylose. Charcoal tablets will be fed as markers, the time taken by the charcoal to make its appearance in the stool being taken as the transit time. Along with the marker, the nutritive grain syrup will be offered ad libitum to each child daily during the study period. In order to ensure supply of essential amino acids, the only other item of food to be allowed will be two eggs, one to each one in the morning and evening daily. Water will also be provided ad libitum. Faecal collections will be started after the appearance of the first marker and will be continued till the appearance of the second marker fed at 72 hours. Urine will also be collected for the same period of time. The stools collected between markers will be pooled and homogenized in a blender. An aliquot from this sample and from urine will be saved for subsequent analyses of nitrogen and calories. Samples from the eggs offered will be saved for analysis of constituents and calories. Any vomitus collected from the patients during the study will also be analysed and subtracted. Serum xylose estimation will be done by the Roe and Rice method (1948). Fat will be estimated by the Van de Kamer method (1949) & total nitrogen content measured according to micro-kjeldahl procedure (Henry, 1964). Adiabatic bomb calorimeter will be used for estimation of calories, benzoic acid acting as the standard. Co-efficients of absorption of nutrients will be calculated using the expression: (Intake-Output) x 100/intkae.

D. SIGNIFICANCE & RATIONALE

The study, if successful and if wheat syrup is available in plenty, should pave the way for reducing the period of hospitalisation and early rehabilitation of malnourished children.

Rice could be equally substituted for wheat. The process of enzymatic extraction is relatively simple if appropriate enzymes (α-amylase and protease now made and available in commercial quantities) are available. Therefore if the results prove to be encouraging further steps may be taken in promoting its manufacture in the country on a cottage industry scale like the soya milk. As a matter of fact the soya milk is produced from imported beans whereas the syrup could be made from either wheat or rice. If the product is found to be acceptable and easily absorbable it should provide an alternative approach for rehabilitating malnourished children with either primary or secondary lactase deficiency. Further studies will be planned on the basis of this initial trial.

E. FACILITIES REQUIRED

1. Children patients in Nutrition Unit, Dacca will be studied.

2. Biochemical procedures will be carried out in ICDDR,B.

F. COLLABORATIVE ARRANGEMENTS

This will be a collaborative study between ICDDR,B & Childrens Nutrition Unit (CNU). The wheat syrup will kindly be provided by Prof. A. Dahlqvist from Sweden.

References:

1. Bengoa J. and Donoso G. (1974). Prevalence of protein-caloric malnutrition, (1963-1973). P.A.G. Bull 4(1): 24.

2. Dahlqvist A., Conrad E., Rockstrom E and Theander O. (1978). A nutritive syrup from grains. Background paper for Fifth Int. Congress on Food Science & Technol., Kyoto, 1978.

3. Henry RJ. Clinical chemistry: principles and techniques. New York, Harper and Row, 1964.

4. Hoyle B., Yunus M. and Chen LC. (1980). Breastfeeding and food intake among children with acute diarrheal disease. Am. J. Clin. Nutr. 33:2365.

5. Lifshitz F., Coello-Ramirez P., Gutierrez-Topete G., Cornado-Cornet MC. (1971). Carbohydrate intolerance in infants with diarrhea J. Pediat. 79:760.

6. Mata LJ (1978). The children of Santa Maria Cauque, A prospective field study of Health and Growth. MIT Press, Cambridge, Mass.

7. Molla AM., Molla Ayesha, Sarker SA. and Rahaman MM. (1981). Intake of nutrient during and after recovery from diarrhoea in children, ICDDR,B Working Paper No. 20.

8. Molla Ayesha, Molla AM., Sarker SA., Khatoon M. and Rahaman MM.(1981). Effects of diarrhoea on absorption of macronutrients during acute stage and after recovery. ICDDR,B Working Paper No. 19.

9. Martorell R. and Yarbrough C. (1981). The energy cost of diarrheal diseases and other common illness in children. Background paper for the workshop on "Interaction of Diarrhea and Malnutrition", Bellagio, Italy, May 11-15.

10. Pollack H. and Sheldon D.R. (1970). The factor of disease in the world food problems J. Am. Med. Assoc. 212:598.

11. Roe JH, Rice EW. Photometric method for determination of free pentoses in animal tissues. J Biol Chem 1948; 173:507-512.

12. Rohde JE.(1981). Therapeutic interventions in diarrhea. Food and Nutrition Bulletin 3:34.

13. Van De Kamer JH, Ten Bokkel Huinink H, Weyers HA. Rapid method for determination of fat in feces. J. Biol Chem 1949; 177:347-355.

SECTION III - BUDGET

1. Personnel Services:	Position	% of Effort	Project Requirement Taka	Dollar
Dr. A.N. Alam	Principal Investigator	20%	14,000	-
Dr. Sultana Khanam	Co-Investigator	-	No cost to ICDDR,B	
Dr. Ayesha Molla	"	10%	7,000	-
Dr. M.M. Rahaman	Consultant	-	-	-
Research Biochemist	-	30%	3,000	

2. Supplies & Materials

Wheat grain syrup - Already provided.

Laboratory tests (in Biochemistry lab) 10,500
(Estimation of calorie, fat, protein, Carbohydrate & d-xylose)

3. Equipment - Nil

4. Hospitalisation cost - Nil

5. Outpatient care - Nil

6. ICDDR,B transport 1,500

7. Rent, Communication - Nil

8. Printing 3,000

9. Travel - Nil

10. Transport - Nil

11. Contractual services - Nil

Grand Total = 39,000
(US $ 1 = Tk. 18) = $ 2164

Abstract Summary for Ethical Review Committee

1. This limited study aims at ascertaining the acceptability and digestibility of a nutrient wheat syrup which could be effectively used for early rehabilitation of recuperating malnourished children in Bangladesh. Malnutrition is the biggest contributor of childhood mortality in developing countries. Rehabilitation of malnourished children is an expensive and long-protracted undertaking. One of the principal difficulties encountered during nutritional rehabilitation of children is the bulk of the food that could supply adequate amount of calories needed. In almost all types of diarrhoea, which is the principal factor associated with childhoood malnutrition in developing countries, absorption of carbohydrates have been found quite satisfactory. Thus a soluble carbohydrate, preferably a polyglucose, should make it possible to concentrate considerable quality of calories in a small volume of water. The nutritive syrup prepared from powered wheat grain is such a carbohydrate, which is easily dissolvable in small volume of water, free from iron, cellulose or lactose and is quite palatable. The acceptability and digestibility of this syrup will be studied on 12 malnourished weaned children between 3 to 5 years of age who are recovering in the Childrens' Nutrition Unit in Dacca.

2. There are no potential risks involved in this study.

3. Though there are no potential risks involved, the patients will be under constant observation of physicians and will get optimum care and management.

4. During data analysis, only the case number will be used.

5. Informed consent in a consent form will be obtained from the authorised legal gardian or the parents of the patient before being included in the study.

6. A brief interview will be taken only to obtain the clinical history of the disease.

7. The patient will get proper treatment and care during the study period, and if successful, will make early recovery. If the wheat syrup proves to be successful then it should pave the way for reducing the period of hospitalization and early rehabilitation of malnourished Bangladeshi children.

8. Hospital records will be required and 1 ml. of venous blood will be obtained for D-xylose absorption test.

CONSENT FORM

The ICDDR,B and CNU are jointly trying to find out better ways of treatment of malnutrition in children. There are different problems involved in treatment of malnutrition. One of the main problems is how to supply adequate amount of calories in a desirable quantity of food. We wish to try a new food, extracted from wheat, which is nutritious, harmless and palatable. We would like your child to participate in our study.

1. Your child will get proper treatment.

2. After an overnight fast, your child will be fed 5 gms. of a sugar, called xylose, dissolved in water, and after 1 hour, 1 ml of venous blood will be obtained. This will not cause any harm.

3. The nutritive wheat syrup will be offered to your child at frequent intervals for 4 to 5 days. Two extra eggs will also be given daily.

4. At the beginning and after 3 days, a harmless charcoal tablet will be given.

5. During this period, stools & urine will be collected for laboratory analysis.

6. Your child will be discharged when recovered completely. If necessary, medicines will be given at the time of discharge.

7. You can withdraw from the study at any time. Even if you do not participate, the treatment of your child will not be hampered.

If you are willing to let your child participate in this study, then please put your signature or left thumb impression below.

_____

Signsture of Investigator

Date: _____

_____

Signature or left thumb impression

Relation _____

with the patient

সম্মতি পত্র

আই, সি, ডি, ডি, আর, বি, এবং সি, এম, ইউ, একযোগে পুষ্টিহীনতা রোগের উন্নততর চিকিৎসা উদ্ভাবন করার চেষ্টা করছে। পুষ্টিহীনতার সঠিক চিকিৎসা করার পথে বিভিন্ন সমস্যা আছে। তার মধ্যে একটি অন্যতম সমস্যা হচ্ছে কি ভাবে পরিমান মত খাদ্যের মধ্যে বেশী পরিমানে ক্যালোরি দেয়া যায়। আমরা সম্প্রতি প্রস্তুত একটি নতুন ধরণের পুষ্টিকর, সুস্বাদু ও নিরাপদ খাদ্য এই চিকিৎসা কার্যে ব্যবহার করতে ইচ্ছুক। আমরা আশা করি আপনার শিশু এই গবেষণায় অংশ নেবে এবং নিম্নলিখিত ব্যবস্থাদি গ্রহণ করা হবে :

১। আপনার শিশুকে সুচিকিৎসা দেয়া হবে।

২। রাতে না খেয়ে থাকার পর পরদিন সকালে ৫ গ্রাম ডাইলোজ নামক একপ্রকার চিনি পানিতে মিশিয়ে আপনার শিশুকে খেতে দেয়া হবে এবং তার এক ঘন্টা পর শিরা থেকে এক সিঃ সিঃ পরিমান রক্ত একবারই পরীক্ষার জন্য নেয়া হবে। এতে আপনার শিশুর কোনরূপ ক্ষতি হবে না।

৩। এই পুষ্টিকর সিরাপটি ৪-৫ দিন আপনার শিশুকে খানিকক্ষণ পর পর খেতে দেয়া হবে। এছাড়া প্রতিদিন দুটো করে ডিম খেতে দেয়া হবে।

৪। শুরুতে এবং তারপর তিন দিন পরে একটি করে চারকোল টেবলেট খাওয়ানো হবে।

৫। এই সময় পায়খানা ও প্রস্রাব পরীক্ষার জন্য নেয়া হবে।

৬। সম্পূর্ণ আরোগ্য লাভের পর আপনার শিশুকে ছুটি দেয়া হবে। প্রয়োজনমত ছুটির সময় ঔষধপত্র দিয়ে দেয়া হবে।

৭। আপনি যে কোন সময় এই গবেষণা থেকে আপনার শিশুকে প্রত্যাহার করে নিতে পারেন। আপনি এই গবেষণায় অংশগ্রহণ না করলেও আপনার শিশুর সুচিকিৎসার কোনরূপ ত্রুটি হবে না।

অপর পৃষ্ঠা-----

আপনি যদি এই গবেষণায় আপনার শিশুকে অংশগ্রহণ করতে দিতে রাজী থাকেন, তবে দয়া করে নিম্নে আপনার স্বাক্ষর অথবা বাম হাতের বুড়ো আংগুলের ছাপ দিন।

গবেষকের স্বাক্ষর

তারিখ----------

স্বাক্ষর

রোগীর সাথে সম্পর্ক----------