INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH

Therapeutic value of coconut oil.

MEMORANDUM

98-021

To : The Chairman, RRC

Date: 14.09.88

From : Dr. Iqbal Kabir
Associate Scientist, CSD

Subject : Review of protocol entitled "Trial of coconut oil based comminuted chicken meat diet in persistent diarrhoea in children - a metabolic balance study," by Drs. P.K. Bardhan et al.

Thank you for sending me the above-mentioned protocol for review. I have already reviewed the protocol in the working group (Prevous review is attached). The investigators have incorporated most of my suggestions. However, I have the following comments:

General comments: The protocol aims to study the efficacy of a coconut oil based diet which basically contains medium chain triglycerides (MCT) and compare that with a soyaoil based diet in persistent diarrhoea in children. The pathophysiology of persistent diarrhoea is still poorly understood and its management is also very difficult. Introduction of a milk free communited chicken based diet at ICDDR,B hospital and elsewhere have shown good clinical recovery in persistent diarrhoea. It has also been shown that replacement of dietary fat by coconut oil (MCT) had a better outcome in chronic diarrhoea like coeliac sprue, cyustic fibrosis and other malabsorption syndrome.

Objectives: The objectives are clear and well-defined. However, I am not sure whether the 2nd objective is directly relevant to the study or patients benefit.

Endpoint = Fat malabsorption

Background: Background is adequate and informative. The investigators have reviewed extensive literature to make the hypothesis stronger. At the end of page 4 the investigator has mentioned about a just concluded study at ICDDR,B which showed significant fat malabsorption in patients with persistent diarrhoea compared to normal controls. How he defined normal control was not clear.

In page 5 the investigators have correctly mentioned about some controversy over the severety of mucosal injury and the clinical course and outcome of persistent diarrhoea. It has also been found that with the improvement of nutritional status the small bowel bacterial overgrowth and mucosal dysfunction are improved without any other interventions. So my point is that this study is basically designed to compare the efficacy of a coconut oil based diet with a soya oil based diet. So justification for some invasive procedures like jejunal intubation or lactose breath hydrogen test seem unnecessary. What conclusion we can make from this study? It is also not possible to understand the exact pathomechanism of persistent diarrhoea

with these limited investigations.

Rationale is well justified.

Specific aims are clear and conform with the study design. However, I have got some reservation about the 3rd objective, the reasons I have mentioned earlier.

METHODS AND PROCEDURE

Selection criteria:

1. Why the investigator has included patients 3-12 month and why not upto 24 month. Does that mean the persistent diarrhoea is not a problem in this agre group?

2. Why the diarrhoea with acute onset will only be included in the study?

Exclusion criteria:

Patient with stool volume < 40 g/kg body weight will be excluded. Why? Does this basal purging rate would imply in cases of persistent diarrhoea as a measurement of severity of disease.

General management: What kind of I.V. fluid will be used to treat dehydration and loss during the entire study period? How the total energy intake 200 ml/kg will be ensured if the patient anoretic. Investigation should include total protein as well.

It is mentioned that a rice suji based diet will be given as a transitional diet at discharge. Whether a baby of 3 month will also get a rice-based diet? Is it a standard diet for a child of that age? I would also request to give the dietary composition of rice-based diet. Because most of the people are not familiar with this diet.

In the composition of diet it is calculated that energy/100 g of chicken based diet is only 50 kcal. I am not sure it is a correct estimation of calorie as used in the hospital.

Sample size calculation: The estimation of sample size was calculated on expecting a mean of 3.75 days duration of diarrhoea after starting the sudy diet. But I think this figure is optimistic rather than actual time will require for cessation of diarrhoea and may not come out with a significant difference.

Follow-up: What is the basis of doing breath H_2 test during follow-up?

References: It was not done in a standard format.

Consent forms: Both the English and Bengali version look clumsy and difficult to understand. Some unnecessary description has stated and no mention about lactose breath hydrogen test. There are a lot of misspelling in Bengali version of consent form and need drastic revision.

Budget is well-defined. However, no mention of patients hospitalization cost.

9

In conclusion this study is very important and will generate new knowledge in the management of persistent diarrhoea if carefully designed. I would recommend its approval.

INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH
GPO Box 128, Dhaka 1000

TO : Dr. P.K. Bardhan

FROM : Dr. I. Kabir DATE: 22/8/88

SUBJECT : Review of protocol entitled "Trial of coconut oil based comminuted chicken meat diet in persistent diarrhoea in children - a metabolic balance study" by P.K. Bardhan et al.

Thank you for sending me the protocol for review. I have gone through the protocol and have the following comments.

General comments: The protocol aims to study efficacy of a coconut oil based comminuted chicken diet in persistent diarrhoea and compare the efficacy with soyabean based diet. There is no doubt that persistent diarrhoea is a major health problem in respect to pathophysiologically and management aspects. The protocol will generate new data if carefully designed.

1. Objectives are clear and well defined.

2. Background is adequate, well written and informative. The investigators have reviewed an extensive literature to make the hypothesis more logical. However I want to emphasis that investigators have not mentioned some of the disadvantages of using MCT for long time. The medium chain fatty acid do not facilitate absorption of fat soluble vitamins nor they provide essential fatty acids. Defficiency of essential fatty acid may lead to dry scally dermatitis, impaired wound healing, susceptibility to sepsis, and thrombocytopenia. Topical application of safflower or sunflower seed oil may reduce the deficiency of essential fatty acids. MCT are also not recommended in patients with a beta lipo proteinemia, which it self may be a cause of chronic diarrhoea.

3. Specific aims are clear. However the 3rd aim does not necessarily essential to attain the study objective. Specially I am concerned about the jejunal intubation. It is well known that some of these chronic diarrhoea patients may have small bowel bacterial overgrowth although it may have little value for the management purpose. It has been shown that with the improvement of the nutritional condition the bacterial count usually goes down. It is also not known if there is any SBO or isolation parasite like giardia from the jejunal fluid whether the investigators are planning to treat these patients with specific antimicrobials, if not is there any strong rational to do an intubation in a sick infants only for the research purpose ,if there is no direct benefit from this invasive procedure.

4. Methods: Patients selection criteria is poorly defined in regards to sex, isolation of known pathogens like Giardia, E. hist., or Shigella whether they will be excluded.

Selection criteria:

- Why patients with diarrhoea of acute onset will be included. Because there is no mention in the procedure.

- There is no mention about the amount of diet (i.e. Kcal/kg.d) will be given. I think this should be uniform and standardized for the both groups. Otherwise the comparisons of nutritional outcome will be difficult.

- How the patients, who failed with study diet will be treated.

- Follow-up: What is the basis of doing breath H_2 test at follow-up.

- The budget section is missing.

I think the study is very important and will generate new knowledge in the management of persistent diarrhoea. I would urge the approval of this protocol.

Thank you.

88-021

INTERNATIONAL CENTRE FOR DIARRHOEAL DISEASE RESEARCH, BANGLADESH
GPO Box 128, Dhaka 1000

TO : Chairman, Research Review Committee

FROM : Dr. M.R. Islam, Reviewer Islam DATE: 6/9/88

SUBJECT : Review of protocol no. 88-021 entitled "Trial of coconut oil based comminuted chicken meat diet in persistent diarrhoea in children - metabolic balance study" - Dr. P.K. Bardhan

Description:

The investigators planned to study 50 male children (3-12 months age group) 25 in each group to compare the impact of a modified chicken-based diet containing either coconut oil or soyabean oil, on nutrient absorption and clinical course in persistent diarrhoea. They also planned to do metabolic balance study for the underlying functional derangements associated with malabsorption in persistent diarrhoea. The intestinal and pancreatic functions will also be evaluated during diarrhoeal state and at convalescent state for correlation with nutrient absorptive capacity. Patient will be studied for 8 days including 72 hours balance study period. Various tests like intestinal permeability tests, breadth hydrogen test, urinary BT-PABA excretion test, Duodenal intubation fluid for microscopy and culture, intensive metabolic balance study etc. will be performed during the study period.

Adequate of background information:

The investigators discussed various factors associated with persistent diarrhoea, with special emphasis on fat malabsorption. As high as 92% of children with prolonged diarrhoea could be associated with fat malabsorption. Studies have shown that digestion, absorption and transport of fats are dependent upon the type of fatty acids attached to glycerol in the triglyceriade molecule. Medium chain triglycerides have been found to be superior than usual dietary fat of Long chain triglycerides.

Critique of the Research plan:

The aims of the protocol is well defined, approach to the problem is valid. The experimental design is adequate, the number subjects to be studied statistically calculated. However, I have the following few comments:

1. In fact, the protocol clearly has two distinct components:
   (a) Metabolic balance study in persistent diarrhoea.
   (b) Comparative clinical outcome study

2. This is not a blind study. Perhaps, it is possible to make blind. It is not clear what appropriate measures will be taken by the investigators to exclude biasness.

3. Coconut oil is being used in many parts of the world as cooking oil particularly South India, Ceylon etc. But to my knowledge the incidence of persistent diarrhoea remains the same as other areas. Hence other factors may play more role than triglycerides alone.

4. How the investigator will record the intake of breast milk? Perhaps by measuring the weight of the child before and after breast feeding. If so special care should be taken during night time when mothers offer breast milk to the child during sleep.

5. Reference for the composition of Diet A and Diet B has not been mentioned. Also references for fatty acid composition of coconut oil and soyabean oil are missing.

6. During follow-up, besides repetition of breath hydrogen test only, perhaps it will be appropriate to repeat other tests like intestinal permeability test, urinary PABA excretion test, Duodenal intubation tests so that patient may act as his own control.

Bengali consent form needs revision and concise.

Budget seems realistic and justified.

I recommend approval of the protocol.

MRI/ra

Dr M Q-K Talukder
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DCH (GLSG) PhD (EDIN) FRCP (EDIN)
Professor of Paediatrics
Division of Nutrition and Gastroenterology
Institute of Postgraduate Medicine and Research
Dhaka-2, Bangladesh
Telephone : 504552, 315500, 310204

88-021

30 August'1988.

Chairman
Research Review Committee
ICDDRB
Mohakhali
Dhaka.

Dear Sir,

Protocol : 88-021 On trail of coconut oil based comminuted chicken diet in persistent diarrhoea in children.

The two objectives of the study are (1) To compare the absorption of MCT rich coconut oil with soy oil in persistent diarrhoea and (2) To examine the likely underlying functional derangements of gut assessed by investigation tests.The objective may only be confined to the therapeutic trail of coconut oil.

In the background information : The definition of persistent diarrhoea should be recast saying." The diarrhoea which starts acutely and persists for over 2-3 weeks with or without growth faltering." The given definition on the protocol has less concensus than the above WHO proposed definition.

Methodology: To fulfill only the first objective of the study,the most of the proposed investigations are unnecessary. The research is not designed to study the pathophysiology.Only the tests necessary for the balance study may be performed.

Comment: I enjoyed reading the protocol.It is an important study. I strongly recommend it aiming only at the first objective and thus abandoning the detail investigative tests which should save time & money.

I am sorry I shall not be able to be present personally at the meeting

Yours Sincerely,

(M Q-K TALUKDER)

INTERNATIONAL CENTRE FOR
DIARRHOEAL DISEASE RESEARCH, BANGLADESH

Memorandum

Dated: 28 / 08 / 1988

TO : Dr/~~Mr/Mrs~~.Iqbal Kabir/Dr.M.R.Islam/
Prof.M.Q-K Talukder

FROM : Chairman, Research Review Committee:

SUBJECT : Critical Analysis of Research Protocol

... Enclosed please find a protocol entitled "Trial of coconut oil based comminuted chicken meat diet in persistent diarrhoea in children - metabolic balance study".

by Dr P.K.Bardhan No. 88-021
Please make a critical review of the research protocol. In doing so, please follow the 'Guidelines for Research Protocol Review', a copy
... of which is enclosed. Please write a brief critical analysis item by item as per the guidelines. Please submit the written critical analysis
RRC Sectt.) to me by 12:00 noon on Tuesday, the 6th September 1988.
The same protocol will be similarly reviewed by two other scientists.

A Research Review Committee meeting will be held on Wednesday, the 7th September 1988 at 2:00 p.m. in the ICDDR,B Lecture Room. One of the critical reviewers will introduce his or her analysis of the protocol and open the discussion. Other critical reviewers will have their input at this moment. I am also circulating the protocol to the Library (to enable any investigator or branch heads to review it) and to the Director and Scientific Associate Directors. Having taken into consideration the three critical reviews and the points brought up by Investigators in the meeting, the Research Review Committee will determine what action should be taken. The Committee may approve the protocol for implementation, it may be returned to the Investigator for revisions or it may be rejected.

Please note that the protocol should have the format as per the enclosed
... 'Format for preparation of protocols'.

Please return the protocol along with your written critical analysis.

Attachments: as stated. (3)

Attachment I.

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Date 23 August 1988
25/8/88

Principal Investigator Dr. P.K. Bardhan Trainee Investigator (if any) _____

Application No. 88-021 Supporting Agency (if Non-ICDDR,B) _____

Title of Study "Trial of coconut oil based comminuted chicken meat diet in persistent diarrhoea in children - metabolic balance study".

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.

(PTO)

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

Pradip K Bardhan
Principal Investigator

_____
Trainee

88-021
25/8/88

SECTION I: RESEARCH PROTOCOL

1.	Title	:	Trial of coconut oil based comminuted chicken meat diet in persistent diarrhoea in children - a metabolic balance study.
2.	Principal Investigator	:	Dr. P. K. Bardhan
3.	Co-investigators	:	Dr. Akramuzzaman Dr. N.H. Alam Dr. R. Haider
4.	Consultants	:	Dr. D. Mahalanabis (Project Co-ordinator) Dr. A. N. Alam Dr. Christine Wanke
5.	Expected starting date	:	As soon as approval is recieved.
6.	Expected completion date	:	18 months after starting.
7.	Total project requirement	:	US $ 81740.00
8.	Source of fund		
9.	Scientific Division	:	This protocol has been approved by the Clinical Sciences Division.

Signature of Division Head : _____

10. Abstract summary:

Persistent diarrhoea is increasingly being recognised as a difficult clinical situation both from pathophysiological and management point of views. Malabsorption of nutrients causing severe nutritional deficit seen in persistent diarrhoea is mostly related to functional derangements of the gastrointestinal tract. The most important aspect of clinical management in persistent diarrhoea is dietary manipulation. In a metabolic balance study, a diet based on coconut oil which is a rich source of medium chain triglycerides, will be compared with an isocaloric similar diet based upon soyabean oil. Fifty children aged 3-12 months and suffering from diarrhoea for more than 2 weeks will be randomly assigned into the two dietary groups. Clinical response and coefficients of nutrient absorption will be recorded, related to the functional derangements as identified by various laboratory investigations, and then compared between the two dietary groups. Subjects will be followed up for 2 months to monitor prognosis and also to ensure appropriate dietary management at home. Data generated is expected to be

useful towards identification of more appropriate and alternative diets as well as to provide insights into the pathomechanism.

11. Reviews :

Research Review Committee _____

Ethical Review Committee _____

Director _____

SECTION : RESEARCH PROTOCOL

A. INTRODUCTION

1. Objective

(a) The major objective of this study is to compare the impact of a modified chicken-based diet containing either coconut oil or soyabean oil as the source of dietary fat upon nutrient absorption and clinical course in children suffering from persistent diarrhoea.

(b) In addition, the study will examine the likely underlying functional derangements associated with the intestinal malabsorption present in persistent diarrhoea, as assessed by investigative tests, and will correlate them with the efficiency of absorption of nutrients.

2. Background

Diarrhoea is one of the major causes of infant and childhood morbidity and mortality worldwide. In most infants and children, the symptoms of acute diarrhoea resolve over the course of a few days and with the advent of effective oral rehydration fluids, the management of such cases has become easier. However, in a small proportion of patients the diarrhoea persists and becomes protracted. Persistent diarrhoea has been defined as more than four liquid stools per day for longer than 2 weeks which may, but not necessarily, be associated with growth faltering. The defination of chronic diarrhoea is more controversial. Some experts find this term appropriate when the infant or child has had diarrhoea for 1 month or more[1].

Studies from different parts of the world have shown considerable variance in the incidence of and multi-factorial association with persistent diarrhoea [2,3,4,5,6,7]. Based on active surveillance data, an estimate of 5-20% incidence world wide of persistent diarrhoea has been made [8].

Post-infectious diarrhoea is probably the commonest cause of prolonged diarrhoea in the developing countries, but much remains to be understood

about the progression of the disease and prologation of diarrhoea[9]. Many consequences of an episode of of acute diarrhoea, such as morphological alterations of the intestinal mucosa, disaccharidase defficiency and breach of the mucosal barriers are factors that may trigger clinical consequences such as intolerances to dietary ingredients and small bowel bacterial overgrowth, which in turn may favor prolongation of diarrhoea with delayed recovery and deterioration of nutritional status[10]. Studies on the microbial aetiology of persistent diarrhoea have shown different proportions of bacterial and viral pathogens isolated from stool, most of which are also capable of producing acute diarrhoea[11]. Also. a broad spectrum of functional disturbances occuring in persistent diarrhoea has been noted, and it appears that the pathogenesis of this syndrome is multifactorial. However it seems that whatever is the primary assult to the intestinal tract, small intestinal mucosal injury highlights the pathophysiology[1].Depending upon the severity of the mucosal damage, changes occur in the digestive, secretory, absorptive and reabsorptive capacities of macro- and micro-nutrients. Two of the most important absorptive problems are carbohydrate and fat malabsorption[11]. The malabsorption of carbohydrates depends upon the extent of the injury to the brush border of the enterocytes, disaccharides being affected more than the monosaccharides. Malabsorption of carbohydrates not only affects net energy absorption, but also stool volume. Unabsorbed carbohydrates, especially mono- and di-saccharides, exerts an intraluminal osmotic force drawing water into the intestinal lumen, thus worsening diarrhoea[11]. Availabilty of unabsorbed crbohydrate substrates inside the intestinal lumen also encourage development of bacterial overgrowth.

Malabsorption of dietary fat is specially important because of its major contribution to dietary energy. Steatorrhoea may also cause defficiencies of the fat soluble vitamins, and may contribute to the severity of diarrhoea because bacterial metabolites of unabsorbed fat are capable of stimulating intestinal secretion. Fat malabsorption occuring in persistent diarrhoea has been documented in several studies[10,12,13,14,15], and can be detected in as many as 92% of children suffering from prolonged diarrhoea[16]. A just concluded study conducted in the ICDDR,B has also confirmed it, where significant fat malabsorption was noted in children suffering from persistent diarrhoea, when compared to normal controls[17].

Among the various steps involved in digestion, absorption and assimilation of fat in intact gut, quantitatively the more important factors are [18] -

a) pancreatic juice : containing lipase, necessary for fat hydrolysis,
b) bile : containing conjugated bile salts, necessary for micelle formation, and
c) intact intestinal mucosa for transmucosal transport .

Among these factors, it is generally accepted that some degree of intestinal mucosal damage can be noted in prolonged diarrhoea, and the severity of the absorptive dysfunction is probably related to the extent of damage to the mucosal integrity[1,19]. However, studies conducted on children suffering from chronic diarrhoea in Indonesia suggested that mucosal damage, as judged by histological examination of biopsy samples, cannot always be detected[20]. It has also been reported that the severity of the small intestinal mucosal injury is not correlated with the clinical course of children suffering from chronic diarrhoea[21].

Fat malabsorption may also occur due to defective micellar solubilisation with diminished intraluminal bile salt concentration, - in some chronic diarrhoeal situations this may happen due to bile salt malabsorption in the entero-hepatic circulation, probably secondary to ileal dysfunction[15,22]. This may also occur in the presence of bacterial overgrowth in the proximal small intestine leading to the formation of free and secondary bile acids because of bacterial deconjugation of bile salts, - as has been suggested to occur in malnourished children suffering from diarrhoea[23]. Various studies has reported the detection of bacterial overgrowth in the jejunum of children suffering from prolonged diarrhoea[24,25,26]. One study has also found that some children suffering from chronic diarrhoea have had their upper jejunum colonised with ETEC and EPEC[27]. However, recent studies have raised questions on the role of intestinal microflora on the pathogenesis of persistent diarrhoea. The results from a peruvian study suggests that the change that occurs in the intestinal microbial flora in persistent diarrhoea is more in the nature of qualitative change rather than quantitative[11].

Pancreatic insufficiency has been observed in several malabsorptive

disorders associated with mucosal injury and diarrhoeas such as sprues [28]. In coeliac disease, pancreatic enzyme output was observed to be insufficient, despite apparently normal pancreas [29], and later it was found that this happens because the nomal pancreas was inadequately stimulated due to diminished release of secretin and cholecystokinin, the two hormones responsible for pancreatic enzyme output as well as biliary output through gall bladder contraction [30,31]. Afterward, it became clear that the mucosal damage also disrupts the endocrine cells present in the proximal small intestinal mucosa, producing this defect [32]. Secondary pancreatic insufficiency leading to protein malabsorption has also been suggested to play a possible role in infantile intractable diarrhoea[33].

Majority of the reports examining the role of different factors upon the intestinal absorptive dysfunction as noted in the chronic diarrhoea syndromes are from the developed countries, where the clinical spectrum is somewhat different than that commonly encountered in the developing countries. The few reports from the developing countries studying intestinal functions in persistent diarrhoea are generally limited to documentation of the nature of dysfunction, without examining the underlying derangement. Knowledge on this aspect will not only help to make clinical interventions more effective, but more importantly will allow to design appropriate diets on a more rational basis.

Whatever the cause and mechanism of persistent diarrhoea, the long term consequences are inadequate nutrition, and impaired growth and organ development[1]. Management of persistent diarrhoea, from the practical point of view, is generally based upon dietary manipulation [12], which has drastically reduced the case fatality rate [34]. Diets free from cow's milk, soyabean or complex carbohydrates are successfully used [35]. Among the different selective diets of such types, chicken meat based diet called 'comminuted chicken' diet is most widely and successfully used, including at the ICDDR,B. The properties of such a diet is the absence of lactose, sucrose, milk- or soya-protein, and complex carbohydrates, which are frequently malabsorbed in persistent diarrhoea. Fat is provided in the form of vegetable oils as butter fat causes significantly less intake and absorption[36].

The digestion, absorption and transport of fats are dependent upon the type of fatty acid attached to the glycerol in the triglyceride molecule. The usual dietary fats are predominantly long chain triglycerides (LCT), i.e., the triglycerides containing fatty acid molecules with chain lengths of 14 carbon atoms or above. The LCTs are fully dependent upon complex biochemical and physiochemical reactions for their assimilation. However, medium chain triglycerides (MCT), i.e., the triglycerides containing fatty acid molecules with chain lengths varying from 6 to 12 carbon atoms, are far less dependent upon these pathways for their assimilation. A comparison is provided below [37].

		MCT	LCT
1.	Intraluminal hydrolysis	Rapid & more complete	Slow, incomplete
2	Water solubility	Bile salts not required	Bile salts & micellar formation required
3	Mucosal uptake	Can enter intestinal cells without prior hydrolysis	Prior hydrolysis and micellar formation necessary
4	Penetration through diseased mucosal surface	More efficient	Inefficient
5.	Intracellular metabolism	MCFA (medium chain fatty acid) formation, re-esterification or lipoprotein synthesis not necessary	LCFA (long chain fatty acid) formation, re-esterification and lipoprotein synthesis necessary
6.	Transport	Independent of lymphatics, - transported in portal vein	Dependent upon lymphatics, - chylomicron transport

Recently it became known that MCTs can be absorbed significantly even from the stomach[38]. It is apparent that MCTs are readily absorbed and assimilated under various conditions, and in addition, it has been demonstrated that MCT therapy results in decreased fecal loss of water and electrolytes [39a,39b,40]. The present indications for MCT therapy include

tropical sprue, non-tropical sprue, small intestinal bacterial overgrowth, pancreatic insufficiency, cystic fibrosis, intestinal resection, hepatic cirrhosis, biliary cirrhosis, biliary atresia, beta-lipoprotein deficiency, and many other conditions[41]. MCTs are also used in intractable diarrhoeas. In an informal trial in the ICDDR,B , substitution of soyabean oil by coconut oil (>50% MCTs) in 28 children suffering from persistent diarrhoea was accompanied by a >20% reduction of duration of diarrhoea[42]. The reasons may be that the abnormal intestinal mucosa leading to secondary pancreatic insufficiency and/or bile salt malabsorption, causes malabsorption of LCTs, which can be bypassed by the MCTs present in cocoanut oil. (Comparison between the fatty acid composition of these two oils are provided in the appendix.)

Based on these observations and reports, the present study proposes to perform a study where the following two points relating to the malabsorption of fats seen in persistent diarrhoea in children will be addressed -

A. Whether partial substitution of dietary LCTs by MCTs (contained in coconut oil) produces improvements in nutrient absorption, recovery of intestinal functions, and clinical course; and

B. What are the underlying functional defects responsible for the malabsorption of fat, and the relative contribution of the different factors in producing this dysfunction.

3. Rationale

Bangladesh is a highly endemic area for diarrhoeal diseases and persistent diarrhoea is becoming more recognised as a serious problem. The clinical management of persistent diarrhoea is not easy, and is based mainly upon dietary intervention and manipulation. This clinical condition is associated with marked malabsorption of nutrients, particularly fat. The underlying pathomechanism is not yet clearly understood. Observations in ICDDR,B hospital indicates that substitution of dietary LCTs by MCTs helps in clinical recovery of patients suffering from persistent diarrhoea. If found effective, it may be usefully applied in the dietary management. In addition, the study may provide useful information on the pathomechanism of nutrient malabsorption, so that other therapeutic interventions could be considered. This study will help to make a more rational approach in

formulating an appropriate dietary and clinical management scheme which will reduce malabsorption of nutrients and the associated risks in persistent diarrhoea in children.

B. SPECIFIC AIMS

1. To estimate and compare fat, carbohydrate and protein absorption during persistent diarrhoea from the defined diets.

2. To assess and compare the impact of the specific diets on the clinical course of the disease.

3. To determine intestinal and pancreatic functions during the diarrhoeal state, and correlate them with nutrient absorptive capacity during the same state.

C. METHODS OF PROCEDURE

Selection criteria :

Age : 3-12 months
Sex : Only male children
Duration of diarrhoea: > 2 weeks but < 6 weeks
Diarrhoea with acute onset

Exclusion criteria

1. Stool volume of less than 40 g/kg body wt. during the first 24 hours of admission (baseline observation period).
2. Presence of complications such as high fever (>38^{o}C), severe infections, electrolyte imbalance, altered level of consciousness, and presence of organisms such as cholera or shigella in stool requiring antibiotics.
3. Clinically apparent severe degree of marasmus (wt for age <55% of NCHS

median wt) or Kwashiorkar.

4. Patients who have recieved antibiotics within the previous 72 hours.

Informed consent will be obtained from the parents/legal guardian before inclusion into the study.

Detailed clinical history will be obtained and a thorough physical examination will be performed including anthropometric measurements (recumbent length, body weight, mid-arm circumference and triceps skinfold thickness). Vital signs will be recorded every 8 hours. Round the clock routine clinical care will be provided, and regular assessment of patients condition will be monitored and recorded.

General management

All hydration including initial hydration will be made by I.V. solutions during the entire study period. During the first 24 hours (baseline observation period), baseline data on stool output, vomitus, food intake, and requirement of I.V. fluids will be obtained, and stool output rate will be calculated. The diet during this period will be half strength milk formula. Breastfeeding will be continued and its intake will be measured.

The eligible patients will be randomly assigned to one of the two dietary groups. In the next 24 h, the patient will receive the study diet (pre-balance period). The oral intake will be restricted upto 200 ml/kg.d. All feed will be given hourly.

Investigations (Routinely performed for persistent diarrhoea patients at ICDDR,B)

1. Blood for CBC, electrolytes, albumin
2. Stool for M/E, Sudan III, helminths and parasites by formal ether concentration, and cryptosporidium
3. Stool for pH and reducing substances, electrolytes and osmolality.

4. Stool for C/S - Campy., Cholera, Shigella, Salmonella and ELISA for Rotavirus. E. coli colonies will be saved and tested for ETEC, EPEC and EAEC; Klebsiella strains will be saved for further evaluation.
5. * Small intestinal intubation for collection of small intestinal fluid for quantitative microbiology and microscopy (for G.lamblia, cryptosporidium and S.stercoralis).
6. * Lactose breath hydrogen test : for detecting lactose malabsorption.
7. Urine] if required
   X-ray]
   Blood C/S]

Special investigations

1. * Urinary BT-PABA test : as a non-invasive method of estimating pancreatic function.
2. * Determination of Plasma secretin and Cholecystokinin (CCK) : to see whether the release of these two hormones (necessary for normal pancreatic function) from the intestinal mucosa, in response to food stimulation, is diminished.
3. * Intestinal permeability test : as measured by differential absorption/ excretion of lactulose and mannitol after a test dose. This non-invasive method is used to assess intestinal function. This test will be performed on admission, and after 7 days to assess change in intestinal function.

(The indication, method, and interpretation of the investigative tests marked [*] are described in the appendix).

Balance study

The study diet will be continued, as started on 2nd day. The amount of diet provided to each patient will be 200 ml/kg/24 hour. At the 48th hour of admission, the first marker as charcoal tablet will be given. A 2nd charcoal marker will be given after 72 h at the same time of first marker. Time of appearance of first marker in stool will be taken as 0 h.

Collection of stool and urine will be started with the appearance of the first marker until 2nd marker comes out. 5 ml of acetic acid will be given in the collecting buckets. 72 h dietary intake will be measured and recorded. All vomitus will be collected in the same way. These samples will be kept at -20°C. Aliquotes of stool samples from homogenized 72 h collection will be taken and analysed for fat[43], nitrogen[44], and carbohydrates by subtracting those from total energy. Total energy content will be determined by calorimetry [45]. Dietary and breast milk contents for fat, CHO and N will also be analysed. Total urinary N_2 excretion/daily will be determined.

$$\text{Absorption coefficient} = \frac{\text{Intake - loss}}{\text{intake}} \times 100$$

Composition of diets/l

	Diet A	Diet B
Ground chicken meat	150.0 g	150.0 g
Glucose	20.0 g	20.0 g
Coconut oil	35.0 g	-
Soyabean oil	-	35.2 g
NaCl	1.0 g	1.0 g
Calcium lactate	0.5 g	0.5 g
$MgCl_2$	0.2 g	0.2 g
H_2O upto	1.0 l	1.0 l
Energy kcal/100 ml	50	50
Osmolality	220	220

As elememtal diets have been shown to cause micro-nutrient defficency in patients suffering from prolonged sickness, a commercially prepared metabolite mixture containing multivitamins and essential minerals will be given to all patients daily for two weeks.

A disadvantage of using MCTs for longtime is the risk of developing

essential fatty acid (EFA) defficiency. To reduce this risk, safflower oil, a rich source of EFAs, will be apllied topically during the period the patients are on study diets.

After recovery from diarrhoea, a transitional diet (half strength rice suzi) will be tried, and if tolerated, the patients will be sent home on this diet.

Use of antibiotics : Patients from whom cholera, shigella or salmonella are isolated on admission (stool culture reports will be available by 48 hours, i.e. before balance period starts) will be transferred from the study and treated with appropriate antibiotics. Patients having E.histolytica (haematogenous form) will not be included in the study and will be treated accordingly. Patients from whom G. lamblia or E. histolytica (cyst form) is isolated, or who have small intestinal bacterial overgrowth as found after culture of jejunal aspirate, will be treated with specific antimicrobials after the study period is finished. Only penicillin, which has got minimal effect upon enteric pathogens, may be used for mild infections during the study period.

Management of patients who failed on study diets : Antibiotics, if indicated as described above, will be given.Management of those patients who fail to respond will be tried by more dietary manipulation through elimination of different dietary components and maintaining parenteral hydration and nutrient support.

Transfer from study : Any child developing sepsis, convulsion, enterocolitis, pnemonia, or any other serious condition will be immediatly transferred to the intensive care unit, and will be excluded from the study. Data upto the point of transfer or deviated course for intervention will be considered in analysis.

Follow up : To monitor the patients' prognosis and also to ensure proper dieatery management, a weekly follow-up for first 2 weeks and then bi-weekly for another 6 weeks will be made. The patients' parents will be asked to come to the hospital for the follow-up check-ups. 6 weeks after discharge, trial with cow's milk test feed will be given during follow-up

visit and the patient observed for 6 hours. A repeat breath H_2 test will be performed at the same time. If tolerated, then transition to normal milk-based home will be advised, otherwise milk-free diet will be continued.

Definations :

1. Diarrhoea - passage of 4 or more liquid motions within 24 hours.
2. Persistent diarrhoea - diarrhoea persisting for more than 2 weeks following an episode of acute diarrhoea.
3. Cessation of diarrhoea - passage of soft stool or formed stool, and no liquid stool in 48 hours.
4. Dietary failure - patients in whom diarrhoea does not stop by 7 days after starting study diet.

STATISTICAL CALCULATION

Calculation of sample size

Expecting the mean duration of diarrhoea with coconut oil based formula to be 3.75 days and that of soya oil based formula to be 4.91 days [42], the sample size is calculated based upon the formula [46].

$$\frac{2\sigma^2(Z_{\alpha/2} + Z_{\beta})^2}{\delta^2} \times (f+3)/(f+1)$$

Wheere σ^2 = pooled variance

δ = difference between the means

and f = degrees of freedom

With the confidence limit of 95% and power of 80%, $(Z_{\alpha/2} + Z_{\beta})^2 = 7.9$. Substituting the values, the calculated sample size is

$$\frac{2 \times 1.31^2 \times 7.9}{1.15^2} \times 29/27 = 22$$

or 44 patients for both groups.

With anticipation of refusals and dropouts, a total of 50 patients will be enrolled into the study.

Data analysis

All data generated from the study will be entered into a microcomputer and appropriate statistical tests will be performed. The two study groups will be compared on admission and pre-randomisation data to assess their comparability. The response variables will be compared after evaluating the distribution so that appropriate tests could be applied. Chi-squared test, Student's `t' test, Mann-Whitney's `U' test, Wilcoxon's Rank/Sum test and multiple regression analysis (keeping co-efficients of absorption of nutrients as the dependent variable) will be considered.

Response Variables

1. Coefficient of absorption of fat, protein and carbohydrate.
2. Stool output (g/kg/24 hrs) over the study period
3. Duration of diarrhoea.
4. Weight gain (or loss) by day 7
5. Amount of I.V. needed (a proxy indicator of diarrhoeal severity)
6. Improvement in intestinal function as measured by intestinal mucosal permeabitlity test
7. Proportion of success in each dietary group
8. Growth rate and morbidity during follow up

Other variables

1. Stool pathogens isolated
2. Presence/absence of small bowel bacterial overgrowth.
3. Presence/absence of lactose malabsorption.
4. Exocrine pancreatic sufficiency/insufficiency.
5. Plasma secretin and CCK level.

Summary of the schedule of investigations and procedures

Day 1

: *Stool tests* - *microscopy*
- *culture*
- *pH and reducing substances*
- *electrolytes and osmolality*

: *Intestinal permeability test*

: *Nutritional anthropometry*

: *Baseline observation period starts*

Day 2

: *Breath hydrogen test (after 4 hour fast) with a test meal containing lactose*

: *Urinary BT-PABA excretion test - Bentiromide will be given alongwith the lactose test meal*

: *Blood tests* - *routine (CBC. electrolytes, albumin)*
- *determination of plasma levels of secretin and CCK (before and 1/2 hour after lactose test meal)*

: *Baseline observation period ends, Pre-balance period starts*

Day 3

: *Duodenal intubation for microscopy and culture (after 4 hour fast)*

: *Pre-balance period ends, Metabolic balance period starts*

Day 6

: *Metabolic Balance period ends*

Day 8

: *Intestinal permeability test*

: *Nutrition anthropometry*

: *Summary assessment of improvement*

APPENDIX

Duodenal intubation [25,47]

Small bowel bacterial overgrowth has extensive, deleterious effects on intestinal digestive and absorptive functions and on the integrity of the small intestinal mucosa, thus contributing to the diarrhoea and malabsorption in protracted diarrhoea. Diagnosis of bacterial overgrowth is made through qualitative and quantitative bacterial culture of small intestinal contents collected by intubation.

Procedure : Intubation of the duodenum will be carried out with a sterile polyethylene tube (diameter 1.5 mm) with a small mercury-filted tip. The test will be performed after 4 hour of fasting in the morning. To facilitate the procedure the children will be premedicated 1 hour before intubation with syp. Phenergan 5 ml and syp. Motilon 5 ml. The tube will be introduced per orally. The passage of the tube through stomach and pylorus into the duodenum will be facilitated by changing the position of the child from left to right side and vice versa. The final position of the tip of the tube will be confirmed by checking the pH of aspirate, it is usually above 6.5. The first sample will be examined microscopically for parasites, particularly G. lamblia, cryptosporidium, and S. stercoralis, and then the next portion will be used for aerobic culture. Dilution of the duodenal juice to the strength of 1:100 and 1:10,000 will be immediately made and each will be plated into Blood agar, Chocolate agar and Mackonkeys agar media for quantitative counts. The organisms isolated will be identified upto genus and if possible upto species level. E. coli isolated will be tested for production of enterotoxins, enteropathogenicity, and enteroadherence. Total bacterial count of 10^5/ml or more will be accepted as indicative of bacterial overgrowth.

Lactose breath H_2 test [48,49]

Secondary sugar intolerance has been found to be associated with a significant proportion of children suffering from chronic diarrhoea, lactose intolerance being the commonest. Breath hydrogen test is a highly efficient test for detecting sugar malabsorption, and is non-invasive, simple, and

relatively easy to perform and interpret. This test was found to be very useful in management of diarrhoeal illness in children by predicting clinical response to dietary change.

Procedure : All expired breath samples will be collected by allowing the child to breathe through a face mask (paediatric size) and a two-way valve into a rubber anaesthesia bag. After a 4 hour fast (sips of plain water will be allowed), a fasting breath sample, for determining baseline H^2 value, will be collected. Then lactose (2 g/kg) will be given to the child and there after intermittent breath samples will be collected every 30 minutes for 3 hours. A portion of the collected sample will be aspirated from the collection bag into a plastic syringe, and H_2 concentration in ppm will be determined with a gas chromatograph, after comparing with a commercial standard of 97 ppm H_2 in air. A rise in H_2 concentration of 20 ppm over baseline will be considered as indicative of lactose malabsorption.

Permeability test [50,51,52]

This is a simple, reliable and non-invasive technique to assess small intestinal mucosal integrity. This method is based upon the estimation of differential sugar absorption where two probe molecules - a monosaccharide and a disaccharide are orally adminstered simultaneously, and urinary recovery of each molecule determined. In diseases of small intestine the recovery of the monosaccharide is reduced, whereas that of the intact disaccharide is increased. Expression of the result as a ratio of disaccharide/monosaccharide urinary recovery seperates between normal and abnormal situations.

Procedure : Permeability tests will be performed on the day of admission and after 7 days. Patients will be offered a freshly prepared drink containing 5 g lactulose with 0.5 g lactose (Duphalac 7.5 ml) and 1 g mannitol in 20 ml of 1% chloroform water. No fasting is necessary, rather breastfeeding and fluid intake will be encouraged. Urine will be collected for 5 hours into uribags. One drop of 20% chlorhexidine gluconate will be added to each bag before collection. Urine volume will be measured and

recorded. Lactulose and mannitol will be measured using an automated enzyme assay system utilising Kobaz-Bio. Results will be expressed as lactulose/mannitol excretion ratio. Normal values are available from ongoing studies in ICDDR,B.

Urinary BT-PABA test [53,54]

This non-invasive test is a widely utilised method to assess and evaluate pancreatic exocrine function, and relies upon intraluminal hydrolysis of an orally adminstered compound N-benzoyl-l-tyrosyl p-aminobenzoic acid (Bentiromide). This compound is selectectively cleaved by pancreatic chymotrypsin releasing free PABA which is then absorbed, conjugated in liver and excreted in urine. Recovery of PABA from a timed urine collection, when expressed as a fraction of the total PABA given, gives an indirect indication of pancreatic chymotrypsin activity and hence pancreatic exocrine function.

Procedure : After a 4-hour fast, a pretest urine specimen will be obtained in order to determine the presence of interfering substances. Bentiromide 15 mg/kg together with p-amino salicylic acid (PAS) will be given in a drink to the patient together with the lactose test meal. A six hour urine collection will be made by collecting urine in uribags. The 6 hour urine volume will be measured and a 20 ml aliquoat will be obtained and analysed by high pressure liquid chromatography[35]. The results will be expressed as the PABA-excretion index (PEI) derived by dividing urinary recovery of PABA by urinary recovery of PAS. The normal value is 4-60, with the median of 19. This test will be repeated after 2 months on selected patients on their follow-up visits to determine the normal value of Bangladeshi children.

Plasma secretin and cholecystokinin

Plasma levels of these two pancreatotrophic enteric hormones will be determined by specific radioimmunoassay methods. Blood sample (2 ml) will

be obtained at the time of blood drawing for routine tests and another 2 ml half hour after the lactose meal. Blood samples will be collected in ice-chilled EDTA-tubes. Plasma will be separated as early as possible and stored at -20^{0} C until assayed. RIA will be done in the lab of Prof. Gyr in Basel, Switzerland. Basal levels of these two hormones as well as the magnitude of release of these hormones after meal will be determined. Normal ranges for Bangladeshi children will be determined from blood samples obtained from nondiarrhoeal age metched children from Dhaka Shishu Hospital.

Fatty acid composition of coconut and soyabean oils

	Coconut Oil	Soyabean Oil
Total fat	99.0 %	98.6 %
Caprylic acid	7.6 %	-
Capric acid	5.7 %	-
Lauric acid	44.7 %	-
Myristic acid	17.1 %	-
Palmitic acid	8.6 %	9.4 %
Stearic acid	2.4 %	3.3 %
Palmitoleic acid	-	0.5 %
Oleic acid	6.7 %	21.7 %
Linoleic acid	1.4 %	52.8 %
Linolenic acid	-	7.5 %.

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Consent form - Coconut Oil Study

Your child is suffering from chronic diarrhoea. ICDDR,B is carrying out a study to evaluate the effect of adding coconut oil to a special diet for your child in the trteatment of chronic diarrhoea. If you agree to enrol your child in this study, the following tests will be carried out, which are routine examinations for the management of chronic diarrhoea.

On the day of admission stool will be examined for microscopy and culture. On the next day, after four hours of fasting, a breath test over three hours will be done before and after giving milk feed to assess the ability of your child in tolerating milk. At the same time 2 ml of blood will be drawn from a vein for determining blood cells, haematocrit, electrolytes and glucose.

Next morning, again after 4 hours of fasting, your child will be intubated by passing a thin plastic tube through mouth into the small intestine, and intestinal juice will be collected and examined for the presence of parasites, worms and bacterias.

Besides, the follwing special tests will be done -

a) On the day of admission, a mixture containing lactulose and mannitol, ehich are harmless drugs, will be given to your child to drink, and then we will collect urine to see what amount of these drugs have come out with urine. This will help us to assess the damage of the small intestine.

b) Likewise, on the second day, Bentiromide syrup will be given to your child to drink, and urine will be collected to detrmine the amount of this drug in urine. We will also collect 4 ml of blood, alongwith the routine blood tests, to check levels of two hormones - secretin and cholecystokinin. By these tests, we will assess the digestive functions of the pancreas.

During this procedures which are safe, your child will recieve a glucose containing intravenous fluid, which will be continued until the study is over.

Careful records of total intake of foods and outputs of stool and urine will be kept. Your child will also recieve the standard diet for chronic diarrhoea containing either soyabean oil or coconut oil according to a previously decided schedule. In addition, a vitamin-mineral mixture will be given daily to your child.

After discharge, follow-up assessments will be done when you will bring your child every two weeks for two months.

If at any time you wish to withdraw your patient from the study, you are free to do so without any obligation, and we will still take care of your child. If the above conditions are acceptable to you, please sign or give your thumb impression below.

Signature of the investigator

Signature/thumb impression of the parent/guardian

Witness : _____

Date : _____

সম্মুখ দৃশ্য

আপনার শিশু দৃষ্টিসম্পর্কী ওষ্টোমিয়ার ভুগছে। আমরা এই ওষ্টোমিয়ার, যে, দৃষ্টিসম্পর্কী ওষ্টোমিয়ার চিকিৎসার আপনার শিশুর জন্য আমরা নিম্নিখিত আধুনিক সংগ্রে নাড়িভেদন টেস্ট মিশ্রিতে তার যথাযথ মূল্যায়ন করার জন্য পরিকল্পনা করেছি, এই পরিকল্পনা আপনার শিশুকে অনুসৃতিক করার জন্য যদি আপনার সম্মুখে আরও তথ্যের দৃষ্টিসম্পর্কী ওষ্টোমিয়ার চিকিৎসার জন্য নিয়মিত ভাবে করনীয় নিম্নলিখিত পরিক্ষাগুলি করা হবে।

ওষ্টোমিয়ার চিন মানের মাংসোমাংসকাশিক্ষ পরিক্ষা ও থালচার করা হবে, পরের দিন, আপনার শিশু কুই সব করছে আছে কি না তা দেখার জন্য হাত খলার আপনার কাপার সহ কুই খেতে দেখার আগে ও পরে তিন ঘন্টা ভিত্তে নিশ্বাসের পরীক্ষা করা হবে, একই সময়ে এক-নাসিক, হেমাটোক্রিট ও রক্ত চিনের মাত্রিমান নির্ণয় করার জন্য একটি শিরা থেকে কুই এমপল রক্ত নেয়া হবে।

পরের দিন সকালে, হাত ধলার আগারাতে আপনার শিশুর মূত্রাশয়ের রস সংগ্রহ করে তাতে পড়ুকে প্রতিরোধ ও কাশির আধিক্য দেখার জন্য আপনার শিশুর মুখের ভিতরে একটি স্প্রে মাত্রায় পদ্ধতি ব্যবহার করানো হবে।

পরীক্ষা, নিম্নের বিষয় পরিক্ষাগুলি করা হবে:—

ক) ওষ্টোমিয়ার চিন, ক্যাথেটার না থাকা কুই অবস্থা যেমন নাসিকাগুলোক ও মাসলেখনের মিশ্রে আপনার শিশুকে স্থান করানো হবে এবং প্রক্রিয়ার সংগ্রে এই ওষুধিগুলো কি পরিমান রোগীর আছে তা দেখার জন্য প্রক্রিয়া সংগ্রহ করা হবে,

খ) একই ভাবে, দ্বিতীয় চিন বিকাল বেলাতেমাসেও আপনার শিশুকে স্থান করানো হবে এবং প্রক্রিয়ার এই ওষুধের পরিমান নির্ণয় করার জন্য প্রক্রিয়া সংগ্রহ করা হবে, বিকালে এক পরীক্ষার অংশে রক্ত কুঁয়ের রসায়ন বিশ্লেষণ ও কার্সিনোম্যোকার্যানের পরিমান জানার জন্য আপনার হাত থেকে রক্ত সংগ্রহ করবো, এই পরীক্ষাগুলি দ্বারা আমরা আপনার পরিমাণ সংক্রান্ত কার্যকলাপ নির্ধারণ করবো।

এখন পর্যন্তই নিয়মিত এবং নিয়মিত করার সময় আপনার শিশুর কিছার জন্য কিছু ঘটনাই দুঃখজনক ওষুধ প্রয়োগ করে এবং পরিবর্তন করে না হয়া পর্যন্ত সেবা যাবে।

দৈহিক পরীক্ষা সময়ে আমার, মল এবং প্রক্রিয়ার পরিমান যথাযথভাবে নিশ্চিতকরণ করা হবে। দূরে নির্দিষ্ট তালিকার অনুযায়ী দৃষ্টিসম্পর্কী ওষ্টোমিয়ার জন্য আপনার শিশু অন্যান্য ওষুধ নাড়িভেদন টেস্টসমূহ নিয়মিতে আসবে আর, এই সময় নিয়মিত ও খালচার সময়ে নিয়মিত আপনার শিশুকে দেখা হবে।

ছুটির পর, ২ ঘন্টার মধ্যে ২ ঘন্টা পর্যন্ত
আমাদের শিক্ষার অবস্থা দেখা হবে,
আমাদের যে কোন সমস্যা থাকলে কোন
পরিস্থিতিতে তাহলে আমাদের সাময়িক সমস্যার মোবাইল
স্যারের কাছে দিতে পারেন তবে তা সম্পূর্ণ আমাদের
আমাদের শিক্ষার শিক্ষাক্রম ক্ষতির, যাতে আমাদের অপূরণীয়
আমাদের কাছে গুরুত্বপূর্ণ হয় তাহলে তখন ফাঁক নিয়ে
আমাদের নাম সুন্দর করে আরো ইন্টারনেটের হাসবেন,

ধন্যবাদের সাথে

ইমামগঞ্জ আরজ
অভিভাবকের স্বাক্ষর/
ইন্টারনেটের নাম

ধন্যবাদ

Consent form - coconut oil study

Non-diarrhoeal patients from Dhaka Shishu Hospital

ICDDR,B is carrying out a study to evaluate if the functions of the intestine and pancreas are normal in young children suffering from chronic diarrhoea. For this purpose we are checking the blood levels of two hormones called secretin and cholecystokinin which are necessary to maintain normal pancreatic function. To determine the normal blood levels of these two hormones, this test will be carried out in children who are not suffering from diarrhoea or any other gastro-intestinal disease.

If you agree to enrol your child in this study, then an additional 4 ml of blood, alongwith the routine blood tests, will be collected from your child to determine the levels of the two hormones. This will not cause any harm to your child.

You are free to refuse without any obligation, and your child will still recieve the care he needs.

If you agree, then please sign or put your thumb impression below.

_____

Siganture of investigator

_____

Signature/thumb impression of the parent/guardian

Witness : _____

Date : _____

সম্মতি পত্র

আমরা নিম্নে স্বাক্ষরকারীরা প্রাপ্তবয়স্ক হয়ে, আমরা এতদ্বারা নেই
ইচ্ছাকৃতভাবে ও সম্পূর্ণ সজ্ঞানে আমাদের ছেলে-মেয়েদের ভর্তি ও
আবাসনের ব্যবস্থাসহ সুবর্ণজয়ন্তী বিদ্যালয় এর মূল্যায়ন প্রক্রিয়ার
জন্য আবেদনপত্রে স্বাক্ষর করছি, সেই জন্য আমরা একে
নিম্নোক্ত ও স্বাক্ষরকারীরা নামের দু'টি হস্তান্তর
করেছিলাম নিম্নে একটি যেখানে আমাদের স্বাভাবিক
কার্যক্রমের জন্য প্রয়োজন, একে দেই দু'টি হস্তান্তর
স্বাভাবিক পরিমাণ কালার জন্য আমরা সব নিম্নে
উপর দেই প্রক্রিয়ার প্রক্রিয়া দেয়া ছেলে-মেয়ে
আমরা আমাদের আমাদের প্রয়োজন নিম্নে প্রস্তুত প্রমুখ
নেই।

যদি এই সম্মতির আমার আমাদের নিম্নে নাম
লিখিতভাবে করতে চাই তাহলে দু'টি হস্তান্তর পরিমাণ
নিম্নে জন্য স্বাভাবিকভাবে নিম্নে হবে সাধারণ সংগ্রহ
আবেদনিক ছাড় সমান হবে আমাদের নিম্নে প্রস্তুত করে
নেয়া হবে, এবং করে আমাদের নিম্নে যেন হয়ে যায়।

আমাদের যেন ব্যক্তিগতভাবে উন্নত স্বাস্থ্যসম্মত করে
সাধন দেয়া তাহলে আমাদের নিম্নে সুযোগসহ ছিন্নিয়ে যাবে,

আমরা নিম্নে ইচ্ছাকৃতভাবে প্রস্তুত নিম্নে।

অভিভাবকের স্বাক্ষর

নিম্নে আমাদের আমরা
অভিভাবকের স্বাক্ষর/
ইচ্ছাকৃতভাবে নাম

তারিখ

ঠিকানা:

COCONUT OIL STUDY: Intake & Output sheet : Balance period

Patient Name: _____ Hosp. #: _____ Date of admission in study : _____

1st Marker given on _____ at _____ 1st Marker out on _____ at _____

2nd Marker given on _____ at _____ 2nd Marker out on _____ at _____

		INTAKE										OUTPUT							BALANCE			
	Body wT.	Comminuted chicken diet					Breast milk					Stool (gm)	Urine (ml)	Vomitus (gm)	N_2	Fat	CHO	Cal	N_2	Fat	CHO	Cal
		Amount (gms)	N_2	Fat	CHO	Cal	Amount	N_2	Fat	CHO	Cal											
Day-1 (1st 24h)																						
Day-2 (2nd 24h)																						
Day-3 (3rd 24h)																						
TOTAL																						
Mean																						
Per kg/ day																						

Water added during blending (ml): _____ 72 hrs stool & urine sample sent on: _____ by: _____

Lab. results: Stool : Fat _____ N_2 _____ Cal _____, CHO _____ Received Lab: _____

Urine : N_2 _____

ICDDR,B
BUDGET PROPOSAL
(In US $)

PARTICULARS

Program name: CSD **Protocol title:** "Trial of coconut oil based comminuted chicken meat diet in persistent diarrhoea in children - metabolic balance study".

P. I's name: Dr. P.K. Bardhan

Protocol no: ..... **Starting date:** 1.9.88

Budget code: ..... **Completion date:** 18 months after starting

EXPENSE CATEGORY			Column A	Column B	Column C	Column D
			1st year Jan.-Dec. (12 months)	2nd year Jan.-Dec. (6 mons)	3rd year Jan.-Dec.	Total Project Cost
A/C No.	Description	Refer Page				
3100	Local Salaries	2	23795.4	14284.8		38080.2
3200	Intl. Salaries	8				
3300	Consultants	14				
3500	Travel Local	15	800	400		1200
3600	Travel Intl.	16				
3700	Supplies & Mat.	18	2184	1001		3185
3800	Other Costs	19	375	175		550
4800	Inter Deptl. Ser.	20	21050	11475		32525
	Total Direct cost		48204.4	27335.8		75540.2
0000	Indirect cost = 31% of total direct cost					
	TOTAL OPERATING COST					
0300	Capital expenditure Refer page no. 21		6200	-		6200
	TOTAL PROJECT COST		54404.4	27335.8		81740.2

Pradip Bardhan
P.I.'s signature

3/8/88
Reviewed by Budget & Finance

ICDDR,B
1988 BUDGET PROPOSAL (IN US $)

DIVISION NAME: CLINICAL SCIENCES DIVISION
PROTOCL/BRANCH NAME: COMPARATIVE TRIAL OF COCONUTE OIL
NAME OF P. I./BRANCH HEAD/DIVISION HEAD: DR.P.K.BARDHAN
BUDGETCODE: STARTING DATE: 1.9.1988
PROTOCOL NO: COMPLETION DATE:
DONOR NAME: GRANT AMOUNT:

EXPENSE CATEGORY			Column A	Column B	Column C		
A/C Code	Description	Refer to Page No.	Actual Jan.-	Estim. Whole	Proposed (12 months)	+	(6 months)
3100	Local Salaries	02			23795.4		14284.8
3200	Intl. Salaries	08			0		0
3300	Consultants	14			0		0
3500	Travel Local	15			800		400
3600	Travel Intl.	16			0		0
3700	Supplies & Mat.	18			2184		1001
4000	Other Costs	19			375		175
4800	Inter Deptl. Ser.	21			21050		11475
	Total Direct Operating Cost				48204.4		27335.8
0300	Capital Expenditure (P.22)				6200		-
	TOTAL DIRECT COST				54404.4		27335

GRAND TOTAL = US$ 81740.00

Description	No. of Positions	No. of Man Months	$ Amount (One year)	+	(for 6 months)
A. Direct Project/Protocol/ Branch Staff at 01.01.1988 (Source: Page 3)	0	0	0		
Add:					
B. New Recruitments (Source: Page 4)	7	70.8	19064.4		11446.8
C. Staff allocated from other area (Source: Page 5)	2	6	4731		2838
(i) Sub Total	9	76.8	23795.4		14284.8
Less:					
D. Separations (Source: Page 6)	0	0	0		
E. Staff allocated to other area (Source: Page 7)	0	0	0		
(ii) Sub Total	0	0	0		
(i) - (ii) TOTAL	9	76.8	23795.4	+	14284.8

	A	B	C	D	E	F=(D x E)		
Job Title	Level	Start Date	No. of positns	No. of Man Mnth	Rate Per Month	$ Amount	+	(6 months)
1.MEDICAL OFFICER	NO-A		1	12	624	7488		4494
2. DIETICIAN	GS-6		1	4.8	518	2486.4		1492.8
3.SR.HEALTH ASST.	GS-4		2	24	263	6312		3792
4.DATA ENTRY TECH.	GS-4		1	6	263	1578		948
5.URBAN VOLUNTEAR			2	24	50	1200		720
6.						0		
7.						0		
8.						0		
9.						0		
10.						0		
11.						0		
12.						0		
13.						0		
14.						0		
15.						0		
16.						0		
17.						0		
18.						0		
19.						0		
20.						0		
21.						0		
22.						0		
23.						0		
24.						0		
25.						0		
26.						0		
27.						0		
28.						0		
29.						0		
TOTAL			7	70.8		19064.4	+	11446.8

MANPOWER-ALLOCATED FROM OTHER AREA (LOCAL STAFF) - 1985

	A	B	C	D	E	F=(D x E)	
Job Title	Level	Budget Code Of Other Area	No.of Positn	No.of Man Months	Rate Per Month	$ Amount	+ (6 months)
1.DR.P.K.BARDHAN	NO-B	11 01 10	1	3	952	2856	1713
2.DR.AKRAMUZZAMAN	NO-A	11 01 10	1	3	625	1875	1125
3.						0	
4.						0	
5.						0	
6.						0	
7.						0	
8.						0	
9.						0	
10.						0	
11.						0	
12.						0	
13.						0	
14.						0	
15.						0	
16.						0	
17.						0	
18.						0	
19.						0	
20.						0	
21.						0	
22.						0	
23.						0	
24.						0	
25.						0	
26.						0	
27.						0	
28.						0	
29.						0	
TOTAL			2	6		4731	+ 2838

Job Title	Travel From	To-From	No.of Persn	Estim. Days of Travel Per Person	Person Days (A)	PerDiem Rate (B)	PerDiem Amount (C=AXB)	Transport Air (D)	Transport Ground (E)	Other Cost (F)	Total $ Amount G= (C+D+E+F)	+ (6months)
VEL COST FOR F.UP PTS							800				800	400
							0				0	
							0				0	
							0				0	
							0				0	
							0				0	
							0				0	
							0				0	
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							0				0	
							0				0	
							0				0	
							0				0	
							0				0	
TOTAL							800				800	+ 400

A/C Code	Item Description	$ Amount (One year)	+	(6 months)
3701	Drugs (used for medicationin the hospitals and field stations)	350		150
3702	Glassware (bottle, beaker, cylinder, petridish, aluminium seal, slides stopper, tube etc.)	80		20
3703	Hospital Supplies (bandage, gauge blade, bowl, cathater, cotton, needle syringe, solution, leukoplast, towel etc.)	150		100
3704	Stationery and Office Supplies (Battery, book register, binders, files, pencil, fastener, paper, ribbon, stapler etc.)	350		150
3705	Chemicals and Media (Acid, reagent dextrose, sodium, bactoagar etc.)	100		50
3706	Materials for Uniform (Cloth, button etc required for making uniforms)			
3707	Fuel, Oil and Lubricants (Diesel, mobil, petrol, kerosene etc.)			
3708	LaboratoSry Supplies (Aluminium foil, bag blade, brush, cap, container, X-ray etc.)	150		50
3709	Housekeeping SUpplies (Aerosol, battary, wiping cloth, duster, lock and key etc.)			
3710	Janitorial Supplies (Bleaching powder, brush, detol, detergent, insecticide, soap etc.)			
3811	Tools and Spares (Automobile spares, tyres, tubes, battery, stores required for maintenance services etc.)			
3712	Non-stock Supplies (Materials not normally kept in stock and purchased only against specific requisitions)	500		250
	Sub Total	1680		770
3713	Freight and other charges (Add 30% to above sub total)	504		231
	TOTAL	2184	+	1001

OTHER COST - 1988

A/C Code	Item Description	$ Amount (One year)	+	(6 months)
3800	Repairs and Maintenance (Maintenance and repairs of vehicles, equipments, furniture and building)	75		25
3900	Rent, communication and utilities (Postage, telephone, telegram, electricity etc.)	100		50
4100	Bank charges			
4200	Legal and Professional Expenses (Professional membership fee, legal fee, audit fee etc.)			
4300	Printing and Publication (Printing of forms, books, journals, reprints etc.)	200		100
4400	Hospitality and Doantion (Guest house accommodation, donations, hospital food, lunch, refreshment etc.)			
4500	Service Charges (porter, labour, washing, laundry and other misc. expenditure)			
4600	Staff Development and Training (Training course fee, training materials, stipend, scholarship, subsistance paid to the staff)			
	TOTAL	375		175

CAPITAL EXPENDITURE - 1988

	Item Description	Manufacturer	No.of Units	Cost+Freight $ Amount (One year)	+ (6 months)
1.	GAS CHROMATOGRAPH		1	3000	
2.	METABOLIC BED		2	1000	
3.	FACE MASK & BREATHING BAG		3	200	
4.	FILE CABINATE		1	150	Nil
5.	DEEP FREEZER			1850	
6.					
7.					
8.					
9.					
10.					
11.					
12.					
12.					
13.					
14.					
15.					
16.					
17.					
18.					
19.					
20.					
	TOTAL			6200	