Attachment I

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

Principal Investigator: Dr. A.K.M. Iqbal Kabir

Application No. 2000- 02

Title of Study: The Efficacy of Fish-oil Supplementation to Pregnant Mothers on Birth Weight of their Babies.

Trainee Investigator (if any): None

Supporting Agency (if Non-ICDDR,B) WB

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 — (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 parents or guardian (if subjects are minor) — Yes (No) N-A

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
   - NA 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

International Centre for Diarrhoeal Disease Research, Bangladesh

Date:

RESEARCH PROTOCOL

FOR OFFICE USE ONLY
Protocol No: 2000-002

RRCApproval: Yes/ No Date:
ERC Approval: Yes/No Date:

1. Title of Project (Do not exceed 60 characters including spaces and punctuations)
The Efficacy of Fish-oil Supplementation to Pregnant Mothers on Birth Weight of their Babies

2a. Name of the Principal Investigator(s) (Last, Middle, First).	**2b. Position / Title**	**2c.**
Qualifications Kabir Iqbal AKM	**Scientist**	**MBBS, Ph.D**

3. Name of the Division/ Branch / Programme of ICDDR,B under which the study will be carried out.
Clinical Sciences Division

4. Contact Address of the Principal Investigator
4a. Office Location: ICDDR,B Hospital Building (2nd floor)
4b. Fax No:
4c. E-mail: kabir@icddrb.org
4d. Phone / Ext: 8811751-60/2331

5. Use of Human Subjects Yes ☐ No ☐
5a. Use of Live Animal Yes ☐ No ☐
5b. If Yes, Specify Animal Species

6. Dates of Proposed Period of Support *(Day, Month, Year - DD/MM/YY)*
Year: January 01, 2000 to December 31,2000

7. Cost Required for the Budget Period
7a. 1st Year ($): 40,198 *2nd Year ($):* *3rd*
7b. Direct Cost ($) 42,755 **Total Cost ($)**

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.

Dr. S.K. Roy (Act) S K Roy — 5/1/2000
Name of the Division Director — Signature — 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 Kabir

Date: 2/1/2000

Table of Contents

Consent Forms in Bangla : Not 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. Iqbal Kabir, MD.Ph.D

Project Name : **Efficacy of Fish-oil Supplementation to Pregnant Mothers on Birth Weight of their Babies**

Total Budget: 42,755 Beginning Date: January 2000 Ending Date: September 30, 2000

PROJECT SUMMARY:

The proportion of low birth weight (LBW) is very high in south Asia, and highest in Bangladesh with a proportion of 40-50%. LBW has increased risk of morbidity, mortality, diminished cognitive function, and increased chronic diseases in adulthood. Therefore, prevention of LBW has been identified as a high priority in south Asia. Several studies have shown beneficial effects of dietary intervention with macro and micronutrients to improve birth weights.

Previous studies conducted in Denmark showed that supplementing fish oil containing n-3 fatty acids (docosahexaenoic and eicosapentaenoic acids) to pregnant mothers significantly increased the birth weight of their newborns. A possible mechanism could be these fatty acids improve transplacental blood and nutrient supply, reduces intra uterine growth retardation.

We propose to conduct a double-blind randomized trial with supplementation of 4 g of fish oil (test) or 4 g olive oil (control) daily during the third trimester of pregnancy. This study will be carried out in Dhaka city with 400 pregnant women identified in the 25th week of gestation by community workers. These community workers will visit the pregnant women at home every day and will ensure compliance by direct supervision. Compliance will be checked by one of the investigators in 10% of cases by a random visit.

Trained nutritionists will be recruited as interviewers for data collection. Baseline data will include socioeconomic, anthropometric, and food intake data (24-h recall and food frequency). Each mother/infant pair will be visited within 24-h of delivery. The outcome variables are birth weight, length, head and chest circumferences of the new born babies. The proportion of LBW will be calculated and compared between the groups.

Results of this study will be useful for planning and implementing health intervention programs aimed at reducing the rate of LBW and improving child survival.

KEY PERSONNEL:

Name	Professional Discipline/speciality	Role in project
1. A.K.M. Iqbal Kabir	Nutritionist	PI
2. Rukhsana Haider	Public Health Nutritionist	Co-Investigator
3. Sayed Akramuzzaman	Epidemiologist	Co-Investigator
4. George J Fuchs	Pediatric Gastroenterologist/Nutrition	Co-Intestigator

DESCRIPTION OF THE RESEARCH PROJECT

Hypothesis to be tested:

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 formation of the hypothesis.

Supplementation with fish-oil (containing long chain n-3 fatty acids) daily to mothers during the third trimester in pregnancy will reduce the proportion of low birth weight by improving trans-placental blood and nutrient supply and by preventing preterm birth.

Specific Aims

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)

The aim of the study is to evaluate whether fish oil supplementation to pregnant mothers during the third trimester of pregnancy.

1. Increase birth weight of their babies
2. Reduces the proportion of Low Birth Weight

Background of the Project including Preliminary Observations

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).

Magnitude of the problem:

Malnutrition remains a major public health problem in Bangladesh with 56% of under five children moderate-severely underweight and 55% of children stunted (BDHS, 1997). A significant proportion of these malnourished children are born with low birth weight (LBW). Approximately one third of all babies in south Asian countries are born with low birth weight (from 19% in Sri-Lanka to 50% in Bangladesh). In Bangladesh, the proportion of LBW is 40-50% (Arifeen 1998, Huque 1991, de Onis, 1998). The proportion of low birth weight reflects the condition of women, and particularly their health and nutrition, not only during pregnancy but over the whole of their childhood and reproductive age.

Consequences of LBW:

Numerous hospital-based studies and a few community based studies in developing countries have provided evidence that low birth weight is an important risk factor for infant death (Das 1993, Ghosh 1983, Mata 1975). In two Bangladeshi studies, about 30% of all neonatal deaths have been attributed to " complications of prematurity" or "small size at birth" (Bhatia, 1989; Islam, 1982). Several other studies in developing countries have also reported mortality risks by birth weight, gestational age and birth weight for gestational age. (Ashworth 1985; Victora , 1987).

Risk factors for LBW:

The many risk factors associated with LBW are of major concern in maternal and child health programs. Interventions directed to the community include health and nutrition education, accessibility to, and improvement of, the quality of health services, and effective nutrition programs directed to the vulnerable groups. The vulnerable groups include teenage pregnancies, under weight women, pregnant women with any risks, such as infections ,anaemia, or a history of LBW in previous pregnancies, social factors; smoking (Sexton 1984), alcohol consumption, and use of drugs. The result of an effective health action, such as food supplementation, nutrition education (Edib K, 1989) and monitoring the nutritional state during pregnancy to ensure satisfactory weight gain, can improve birth weight. It can also increase the probability of successful breastfeeding and resistance of infants to certain diseases.

Weight gain in pregnancy: Maternal weight gain appeared to be a strong predictor of baby's birth weight (Naeye 1990). Maternal weight gain, prepregnancy weight, birth weight of last child were major determinants of birth weight (Kramer, 1987; Falkner 1981, Farraz 1990). The importance of satisfactory weight gains in pregnancy has been stressed in several studies. On an average a normal healthy woman should gain about 12 kg during pregnancy. In Bangladesh the average weight gain of women during pregnancy has been reported to be 4-5 kg only (Choudhury 1987).

Length of gestation is an important determinant of LBW. Studies from developing countries have shown incidence of preterm and low birth weight to be 5.7% to 9.2% (Ghosh 1983). In Bangladesh a perinatal survey was conducted in four different locations, an urban hospital and a clinic, a rural hospital and rural home deliveries (Canosa, 1989). The study showed that 48-82% of LBW were IUGR. In another study in rural Dhaka 6.1% of birth were premature (<37 week) and 12.7% were growth retarded (< 37 weeks and < 2000 g) (Hort 1987).

Effects of nutrient supplementation to pregnant women to prevent LBW:

Recent evidence shows that poor nutrition around the time of conception is associated with low birthweight and reduced head circumference. There is wide range of nutrient deficits in the habitual diets of women of childbearing age. Deficiencies of dietary energy, B vitamins, magnesium, zinc, and essential fatty acids (EFA), all correlate with low birth weights.

Only few studies have indicated a positive effect of dietary supplementation on increased weight gain in pregnancy (Ceesay 1998, Mardones-Santender, 1988; de Onis, 1998). In a research program of the INCAP, the provision of additional foods (20,000 calories during pregnancy) to pregnant women in four villages in Guatemala resulted in an increase of mean birth weight from 2,997 g to 3,114 g (Lechtig, 1975). Studies from other developing countries (Bhatnagar,1981; Mora, 1979) also reported increase in birth weights after food supplementation to pregnant women.

In contrast some studies could not show any effect of supplementing additional energy and protein (Kusin 1992) or other micronutrients on birth weights (de-Onis, 1998 ; Mahmoud, 1989; Hunt 1985, Osendarp 1998). This may be due to the fact that several factors affect the birth weights.

de Onis recently summarizes the evidence from randomized controlled trials of the effectiveness of nutritional interventions to prevent intra uterine growth retardation. Of the 12 nutritional interventions reveiwed (de Onis Eu J clin nutr,1998) only balanced protein-energy supplementaion seems to marginally improve mean birth weight and decrease the number of LBW babies. The modest benefits achieved on fetal growth may be explained by rather small increases in net energy intake acheived in these trials. Non-compliance and dietary replacement could play a role in these small increases in birth weight. In a recently conducted operations research in the Bangldesh Integrated Nutrition Project where pregnant women were supplemented with 600 kcal per day, could not show any significant reduction in LBW (personnal communication). This could be due to non-compliance and perhaps replacement of dietary intake, the median duration of supplemenation was 90 days.

Effects of dietary fatty acids in pregnancy:

The fetus and placenta are fully dependant on maternal essential fatty acid (EFA) supply for their growth and development. The diet before pregnancy plays an important role in determining maternal EFA status since these essential nutrients are stored in adipose tissue and can be mobilized over time through lipolysis. The major fat deposition occurs during the third trimester but key phospholipids in placental vessels and uterine vasculature are dependent on EFA supplied by the mother for eicosanoid formation.

During third trimester, fetal fatty acids demands are high. The fetus requires lipids for cell and organ growth, as well as for storage for future metabolic needs during immediate postnatal period. Both transplacental transport of fat and fetal lipid synthesis are required prenatally to meet these demands. During late fetal life and early newborn development, specialized functions of tissues, such as brain and lung, heighten these lipid requirements.

The placenta selectively transports arachidonic acid (AA) and docosahexaenoic acid (DHA) from the maternal to the fetal compartment. Thus there is an enrichment of these long chain PUFAs in circulating lipids in the fetus especially during the third trimester when fetal demands for neural and vascular growth are greater (Simopoulos, 1991). A total of 600 g of EFAs are transferred from mother to fetus during a full length of gestation; net uptake approximate 2.2 g per day. Nevertheless, recent studies by Holman (1991) suggests that in fact *w*-3 long chain PUFAs decrease during pregnancy and lactation in women from Minnesota, USA. Similar data have been obtained from Europe (Honstra, 1990). A possible need for *w*-3 PUFA and specifically DHA supplementation during pregnancy is suggested by these results.

Role of EFA in improving trans-placental nutrient supply:

Nutrients from the mother are transported to the fetus through umbilical vein, and blood flows back from the fetus to the mother via umbilical arteries. Since the umbilical vessel walls do not have a *veso vasorum* to obtain their nutrient supply, they obtain their nutrients directly from the blood flowing through them. Therefore, the EFA composition of umbilical venous walls is considered to be long-term reflection of the EFA supply from mother to fetus, whereas the fatty acid composition of the arterial vessel walls is likely to reflect the EFA status of the tissue of the developing fetus. In a prospective study concentrations of *w*-3 fatty acids including docosahexaenoic acid and eicosapentaenic acid in the umblical vessel wall were significantly lower in SGA growth retarded babies than SGA normal growth and AGA babies (Felton et al 1994).

Recent studies have shown that average birth weight of babies in Faroe Islands was about 230 g higher than the Danish babies (Olsen 1985). The high birthweight in the Faroe Islands suggests that a high intake of fat from fish and whales, rich in long-chain n-3 fatty acids, prolongs gestation and thereby reduces the preterm births (Olsen, 1986). Dietary long-chain n-3 fatty acids could delay premature delivery in two ways. Firstly, they could delay initiation of labour and cervical ripening by inhibiting the production of prostaglandins F2 and E2. Secondly, they may relax the myometrium by increasing the production of prostacyclines (PGI-2, and PGI-3). Although the postulated mechanism of increased birth weight in Faroe Islands was due to pro,onged gestational period (Olsen, 1985), another study showed the mean birth weight was about 170 g higher in Fish-oil supplemented group than non-supplemented even the gestational age was same (Houwelingen AC 1995). Thus their result suggests that

there might be other mechanism such as improved transplacental nutrient supply caused increased in birth weight.

In addition to increasing birthweight, fish-oil supplementation has also been found to reduce the occurrence of pregnancy-induced hypertension and pre-eclampsia (Secher &Olsen 1990). Moreover, the fetus seems to have a high requirement of docosahexaenoic acid DHA (Honstra 1990), which is essential in fetal brain development.

We therefore, hypothesize that dietary (n-3) PUFA will increase birthweights by improving nutrient supply through placenta and reducing preterm birth. As incidence of low birthweight in developing countries is substantially high, reducing number of LBW will have a substantial impact on childhood morbidity and mortality and thereby improve child survival strategies.

Research Design and Methods

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 or 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).

STUDY DESIGN AND METHODS:

The study is a double-blind, controlled, randomized trial starting in the third trimester of pregnancy, and continuing until delivery. A brief outline of the study procedure is described below:

STUDY PROCEDURE:

Stage I: Recruitment and training of study personnel.
Stage II: Identification of pregnant mothers.
Stage III: Base line data collection.
Stage IV: Supplementation of fish-oil to pregnant mothers.
Stage IV: Data collection at delivery and follow-up visits.

SAMPLE SIZE CALCULATION:

Sample size was calculated using available data in order to detect differences between treatment groups with 80% power and 95% significance. Recent data (UNICEF 1998) shows that the prevalence of low birth weight in Bangladesh ranges from 30-50%. Taking 40% as median the we expect to reduce the incidence of LBW to 25%, the required sample will be 152 in each group, with 30% drop out, migration and confounders the total sample size in each group will be 198, and for two groups 400.

Formula used to calculate the sample size is;

$$n = \frac{p1\,(100-p1) + p2\,(100-p2)^2}{(p1-p2)^2} \times \alpha\beta$$

Where p1 is proportion of low birthweight in the control (40%), p2 the expected birth weight by intervention (25%). $\alpha\beta$ for 95% probabilty and 80% power.

Recalculation of sample size: As advised by one of the member of the RRC, I have recalculated the sample size on the basis of mean body weight. From our previous study from the same area the mean $\pm$ SD birth weight were 2700 $\pm$ 380 gm. Utilizing the formula from Betty Kirkwood (see below), the required sample size is 250. However, as we are also interested to reduce the proportion of LBW by intervention the sample size calculated with 15% reduction in LBW is 400. So a total of 400 subjects will be studied.

$$n = \frac{(u+v)^2) + \delta^2{}_1 + \delta^2{}_2}{(\mu_1 - \mu_2)^2}$$

Subjects:

Women will be eligible if the following criteria are met:

-pregnant women at 25th weeks of gestation.
-age between 18-40 years.
-parity maximum four.
-intention to stay in the area for the delivery and written consent for the study.
- no documented record of heart diseases, diabetes mellitus, or previous history of eclampsia
- no history of allergy to fish.

Location of the study:

The study will be done in Badda in Dhaka city, which is 6 km from ICDDRB. The population of this community is about 200,000 with mostly lower middle class and lower socioeconomic class. We have recently conducted a study in this area and found on an average 150-200 deliveries take place every month.

RANDOMIZATION, BLINDING AND FISH-OIL SUPPLEMENTATION:

A structured questionnaire will be administered at the beginning of the third trimester of pregnancy to collect socioeconomic data, length of gestation, antenatal care, any complication during previous pregnancy, and any medical problem.

When entering the study, at 25th weeks of pregnancy, the women will be randomly assigned into two groups. The randomization procedure will be stratified to ensure equal distribution of women according to previous pregnancies as parity is an important potential confounder. The study will be double-blind, therefore registration of women will be done by random number derived from a random number table with a block size from 4-8. The women will receive the assigned capsule according to the number which will contain fish-oil or a olive-oil.

After enrolment four capsules (each containing one g of fish-oil or olive oil) per day will be given to the pregnant women until delivery. The fish-oil capsules containing (32% of eicosapentaenic acid, 23% of docosahexaenoic acid) and olive oil capsule will be indistinguishable in appearance.

STUDY PROCEDURE AND SPECIFIC TASKS:

Community workers:

Mothers with personal breastfeeding experience and some literacy, motivated to help other mothers breastfeed successfully, and residing in the area will be identified to work as community workers (CWs). We already have such women trained as peer counsellors from our previous study.

Pregnant women will be identified by the CWs in the area, who will supply the capsules to the mother every week. The community workers will visit the pregnant women daily and ensure the compliance by direct supervision. Regular compliance checks will be done by unexpected visits in a 10% sample. In addition to providing capsules the CWs will also provide breastfeeding counselling, and other nutrition counselling to take more food during pregnancy to both the groups of mothers. They will also provide practical help to the mothers to initiate breastfeeding immediately after delivery.

Field Research Assistants (FRA):

Female with M.Sc in nutrition will be recruited as field research assistants (FRA), who will also be responsible for calculating gestational age by last menstrual period (LMP) and obtaining anthropometric data. FRAs will be trained by the investigators with regards to techniques for interviewing, filling questionnaires and anthropometry. Precision, accuracy, inter and intra-observer error will be measured using standardized techniques which will be repeated every three months during the field work.

The FRAs will visit the mothers just after enroling the pregnant women and will obtain baseline data including socioeconomic, anthropometry. They will visit the mothers every month for collection of anthropometric data as well as mothers' dietary history by 24-h dietary recall method.

The FRAs will visit the pregnant women at about 6 months of pregnancy to explain the study objective and enrol them. The method of immediately notifying her pregnancy outcome will be explained to the pregnant woman. She will be given a 'referral card" which includes her name, an identification number, household address (or location), and expected date of delivery. A household member will be identified who will notify the woman's delivery by bringing the card to the Centre. If no household member is able to notify, then the woman will be asked to identify a close friend or neighbour living nearby who can be requested to notify the birth. The family notifier will be reimbursed for the travel cost.

Details of Data collection at each visit

Each mother-child pair will be visited within 72 hours of delivery. Information will be collected at these visits are as follows.

* The newborns will be physically examined to detect congenital anomalies. LMP will be used to assess the baby's gestational age.

* Body weight, length, head, arm, and chest circumferences of the newborn will be obtained with standardized equipments. The age of the child in hours will also be noted.

* Information on perinatal events; delivery status, mode , location of delivery, any complication during delivery, live or still birth, if dead; cause of death.

* Information on feeding status of baby

Outcome variables

1. Infant's status at birth:

   a) Birth weight,
   b) Length,
   c) Gestational age
   d) Head circumference
   e) Chest circumference

2. Maternal factors:

   a) Body weight,
   b) Height,
   c) MUAC,
   d) Body mass index (BMI)
   e) Pregnancy related complications.

Significance and Rationale:

The proportion of low birth weight in Bangladesh is highest in the world. These LBW babies can not catch-up and attain their optimal growth during the later life. Due to the inappropriate feeding practices and recurrent infections these babies remain undernourished and have poor physical and cognitive development.

The problem of malnutrition perhaps starts in mothers' womb due to poor nutritional status of women in the developing countries. Many babies are born preterm (< 37 weeks of gestation), and who are born full term are also low birth weight. The prevalence of low birth weight is very high in the developing countries particularly south Asia.

Although many supplementation trials have been conducted with energy and macronutrients in many developed countries, however, only few studies have been done in developing countries. There are variable effects in these studies. No study has been done to

evaluate the effects of supplementing EFA to pregnant women on birth weight in developing countries, where problem of LBW is greatest.

Results of this study will allow us to evaluate whether supplementation of EFA to pregnant women will increase the birth weight and reduces the rate of LBW. Information derived from the proposed study will be essential for planning and implementing health intervention programs aimed at reducing the incidence of low birth weight, and improving infant growth and child survival.

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 equipment 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).

LOGISTICS:

The study will be done in an urban community in Dhaka (Badda), approximately 6 km from the Centre (ICDDR,B).

Female attendant (FA) will be recruited who will accompany the study interviewer on all visits. The FA will not only assist in carrying the equipments but also help during the actual measurements.

Some of the births in this population may take place in hospitals and clinics in Dhaka city. The most likely institutes will be identified and arrangements will be made with them for collecting information on birth weight, and allowing our interviewers to visit the mothers and baby for anthropometry and for collecting information on morbidity and mortality during the stay in these institutions.

Referral:

All infants requiring treatment will be referred to the nearest health care facilities. If the office is notified of an emergency (before, during or after delivery), or interviewer encounters any problem during her visit, then the woman and/or her baby will be immediately referred to the nearby health facilities or hospitals.

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 management and analyses plan:

The questionnaires and data forms will be reviewed and edited on regular basis for completeness and accuracy. If necessary, an interviewer will revisit the household for clarification or missing information. Data will then be entered into the computer using EPI-Info Statistical Package. A program incorporating range and consistency checks will be used for data entry. Data will be periodically checked using frequency distributions and cross-tabulations to identify outlier.

Descriptive statistics (mean, standard deviation, median, variance) will be used to assess the distribution characteristics of the dependant and independent variables. The means of continuous independent variables will be compared using t-test. For categorical variables chi squared test or other appropriate test will be used. Logistic regression will be used to assess the simultaneous effect of multiple independent factors on the dependent variables.

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.

The study as indicated earlier will evaluate the efficacy of fish-oil supplementation to pregnant mothers to reduce low birth weight. The study subjects will be informed about the study objectives, procedure and potential benefits of the study Consent will be obtained from the subjects to protect the subjects rights.

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

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.

REFERENCES

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Dissemination and Use of Findings

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 program.

The findings will be disseminated at ICDDR,B seminars, international conferences. Papers will be published in International Nutrition Journals.

Collaborative Arrangements

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).

None

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	Date of Birth	Position
A.K.M. Iqbal Kabir		Scientist Clinical Sciences Division

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

Institution and Location Field of Study	Degree	Year	
Dhaka Medical College Dhaka University, Bangladesh	MBBS	1973	
Institute of Nutrition and Food Science, Dhaka University, Bangladesh	Ph.D	1992	

Research and Professional Experience

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).

1.	1993-Present	Scientist, CSD
2.	1987-92	Associate Scientist
3.	1984-86	Research Associate Case Western Reserve University Cleveland, USA

Bibliography:

SOME SELECTED PUBLICATIONS ON NUTRITION:

1. Kabir I, Malek MA, Mazumder RN, Rahman M, Mahalanabis D. Rapid catch-up growth of children fed a high protein diet during convalescence from shigellosis. Am. J. Clin. Nutr 1993;57:441-45.

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5. Rahman MM, Kabir I, Mahalanabis D, Malek MA. Decreased food intake in children with severe dysentery due to Shigella dysenteriae-1 infection. Eur J Clin Nutr 1992;46:833-8.

6. Alam AN, Chowdhury AA, Kabir I, Sarker SA, Rahman MM. Association of pneumonia with undernutrition and shigellosis. Indian Pediatr 1984;8:609-13.

7. Stoll BJ, Banu H, Kabir I, Molla A. Night blindness and vitamin A deficiency in children attending a diarrhoeal disease hospital in Bangladesh. J Trop Pediatr 1985;1:36-39.

8. Banwell JG, Howard R, Kabir I, Adrian TE, Diamond RH, Abramowsky C. Small intestinal growth caused by feeding red kidney been phytohemagglutinin lectin to rat. Gastroenterology 1993;104:1669-77.

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10. Haider R, Islam A, Kabir I, Habte D. Early complementary feeding is associated with low nutritional states of young infants recovering from diarrhoea. Trop Pediatr 1996;42:170-2.

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12. Mazumder RN, Kabir I, Rahman MM, Khatun M, Mahalanabis D. Absorption of macronutrients from a calorie-dense diet in malnourished children during acute shigellosis. J Pediatr Gastroenterol Nutr 1996;23:24-8.

13. Khaled MA, Kabir I, Goran MI, Mahalanabis D. Bioelectrical impedance measurements at various frequencies to estimate human body composition. Indian J Exp Biol 1997;35:159-61.

14. Haider R, Kabir I, Hamadani J, Habte D. Reasons for failure of breastfeeding counselling mothers' perspective in Bangladesh. Bull WHO 1997;75:191-6.

15. Hussain I, Kabir I, Fuchs G, Alvarez JO, MacCutcheon R, Khaled MA. Intra and extra cellular water dynamics on rehydration in cholera and non-cholera patients. Dig Dis Sci 1997;43:663-67.

16. Kabir I, Rahman MM, Haider R, Mazumder RN, Khaled MA, Mahalanabis D. Increased height gain of children a high-protein diet during convalescence from shigellosis: a six months follow-up study. J Nutr 1998;128:1688-91.

17. Haider R, Kabir I, Ashworth A. Are breastfeeding messages influencing mothers in Bangladesh? J Trop Pediatr (in press)

18. Haider R, Kabir I, Fuchs GJ, Habte D. Neonatal diarrhoea in a diarrhoea treatment centre in Bangladesh; clinical presentation, breastfeeding management and outcome. Indian Pediatr (in press)

19. Islam S, Kabir I, Wahed MA, Goran MI, Mahalanabis D, Fuchs G, Khaled MA. Multifrequency bioimpedance analysis to assess human body composition. Nutr Res 1999;19:1179-88.

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. Rukhsana Haider	Associate Scientist	25 November 1951

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

Institution and Location	Degree	Year	Field of Study
Fatima Jinnah Medical College, Lahore, Pakistan	MBBS	1975	Medical Science
London School of Hyg. & Trop. Med. Univ. of London	M.Sc.	1989-90	Human Nutrition
London School of Hyg. & Trop. Med.	PhD	1998	Public Health Nutrition

Research and Professional Experience

Associate Scientist, ICDDR,B from 1994 till date.

Acting Coordinator, BINP-ORP (Bangladesh Integrated Nutrition Project - Operations Research Project) July - Sept. 1999.

Part-time Consultant, UNICEF, 1992-1995.

Assistant Scientist, ICDDR,B, 1992-1994.

Medical Officer, ICDDR,B, 1984-1992.

RECENT PUBLICATION (no more than five).

1. Haider R, Kabir I, Fuchs GJ, Habte D. Neonatal diarrhoea in a diarrhoea treatment centre in Bangladesh: clinical presentation, breastfeeding management and outcome. Indian Pediatrics (in press)
2. Haider R, Kabir I, Ashworth A. Are breastfeeding messages influencing mothers in Bangladesh? Results from an urban survey in Dhaka, Bangladesh. *J Trop Pediatr* (in press)
3. Roy SK, Tomkins AM, Haider R, Behrens RH, Akramuzzaman SM, Mahalanabis D, Fuchs G. Impact of zinc supplementation on subsequent growth and morbidity in Bangladeshi children with acute diarrhoea. *Eur J Clin Nutr* (in press)
4. Haider R. Impact of peer counsellors on breastfeeding practices in Dhaka, Bangladesh. PhD thesis, London School of Hygiene and Tropical Medicine, UK, 1998.
5. Kabir I, Rahman MM, Haider R, Mazumder RN, Khaled MA, Mahalanabis D. Increased height gain of children fed a high-protein diet during convalescence from shigellosis: a six-month follow-up study. *J Nutr* 1998;128:1688-91.

Detailed Budget for New Proposal

Project Title : **Fish-oil Supplementation to Pregnant Mothers on Birth Weight of their Babies**

Name of PI: Dr. A.K.M. Iqbal Kabir

Protocol Number | Name of Division : CSD

Funding Source : WB (NCOE) | Amount Funded (direct): 40,198 | Total :
Overhead (%)

Starting Date: | Closing Date:

Strategic Plan Priority Code (s) :

Fish Oil Study
P.I: Dr. I. Kabir

		% Effort	in US$ 1st Yr
Local Salaries		30	
Dr. Iqbal Kabir (# 1345-8)		20	
Dr. R. Haider, Co-Investigator		10	
Dr. S.M. Akramuzzaman			
Sr. B.F. Counsellor (GS-5)-1 (4546-8)			
Personnel (New)			
Field Research Assistant (GS-4)-6		100	15,055
Data Coding Assistant (GS3)-1		100	2,099
Field Attendant @ $42/m-3/6		100	2,268
Peer Counsellors @ $30/m-15		100	4,050
One Ward Attendant (GS1)			1,583
	Sub-total		**25,055**
Consultant			
	Sub-total		
International Travel (For presenting Study Findings at Seminar/Conference) Ticket cost, per diem etc.			
	Sub-total		
Local Travel			
Transport for follow-up data collection			5,000
	Sub-total		**5,000**
Supplies and Materials			
-Office supplies			1,000
Non-stock (Med,Fish oil)			9,000
Medical equipment ((Freight Charge)			1,000
	Sub-total		**11,000**

Other Contractuals		
Fax, DHL,E-Mail, Postage		1,000
Printing and Publication		500
Training		
	Sub-total	**1,500**
Interdepartmental Services		
Local Transport		
Xerox, Med Illustration, Library Services		200
	Sub-total	**200**
Capital Expenditure		
Computer with printer and accessories		
Weighing scale (Seca), Length Board		
	Sub-total	
Total Direct Cost		**42,755**

Budget Justifications

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

Personnel: Salary support for Principal Investigator and other Co-investigator have not been charged as they are supported by WB/NCOE budget.

Salary for only new personnel are required.

Supplies:

To purchase fish-oil/olive capsules for 400 pregnant women daily for 90 days about 1,44,000 capsule will be required and US$ 10,000 has been budgetted including freight charge.

Other Support

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)

Time Schedule for the Protocol (Year 2000)

		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1.	Recruitment of study personnel and training												
2.	Enrollment of Study subjects												
3.	Data Collection and Entry												
4.	Analysis and Report Writing												

APPENDIX

International Centre for Diarrhoeal Disease Research, Bangladesh

Voluntary Consent Form

Title of the Research Project: The Efficacy of Fish-oil Supplementation to Pregnant Mothers on Birth Weight of their Babies.

Principal Investigator: Dr. A.K.M. Iqbal Kabir

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.

The proportion of low birth weight (LBW) is very high in Bangladesh and contributes to malnutrition and increased child morbidity and mortality. Different studies have shown that dietary supplementation with food and other nutrients improves birth weight. Previous studies done in developed countries have shown that supplementing with Fish-oil containing w-3 fatty acids improves birth weight substantially. However, no study has been done to evaluate the impact of fish-oil supplementation in developing countries where LBW is high.

We are therefore going to study whether fish-oil supplementation to pregnant mothers during the third trimester can reduce low birth weight of their babies. If you agree to participate to our study one community worker will come and visit you daily and give four capsules of fish-oil or olive oil. You need to take the capsules every day until your baby is delivered. One field research assistant will come and visit you to have some information. They will also visit you every month take your body weight. After the delivery of your baby your family member will be given a card and you will be asked to report the delivery immediately to CWs. A field research assistant will visit and will take your baby's weight, length.

If you agree to participate please give your signature here.

Signature of the FRA

Date

Signature/Thumb Impression of the mother

Date

আন্তর্জাতিক উদরাময় গবেষণা কেন্দ্র
মহাখালী, বাংলাদেশ

সম্মতি পত্র

গবেষণার নাম ঃ গর্ভবতী মায়েদের মাছের তেল খাইয়ে শিশুদের জন্মওজন বৃদ্ধির কার্যকারীতা

পৃথিবীতে স্বল্প ওজনের শিশু জন্মের হার বাংলাদেশে সর্বোচ্চ এবং স্বল্প ওজনের শিশুরা অপুষ্টি ও শিশু মৃত্যুর হার বাড়ায়। বিভিন্ন গবেষণায় দেখা গিয়েছে যে, গর্ভবতী মায়েদের অতিরিক্ত খাবার ও পুষ্টি দিলে শিশুর জন্ম ওজন বৃদ্ধি পায়। উন্নত দেশের গবেষণায় দেখা গিয়েছে যে, গর্ভবতী মায়েদের মাছের তেল খাওয়ালে শিশুর জন্মওজন বৃদ্ধি পায়। কিন্তু উন্নয়নশীল দেশে এই গবেষণা কখনো হয়নি, যেখানে স্বল্প জন্মওজন একটি মারাত্মক সমস্যা।

অতএব, আমরা গবেষণা করে দেখতে চাই যে, আমাদের দেশে গর্ভবতী মায়েদের শেষ তিন মাসে মাছের তেল খাওয়ালে শিশুর জন্মওজন বৃদ্ধি পায় কিনা। আপনি যদি এই গবেষণায় রাজী থাকেন একজন স্বাস্থ্যকর্মী আপনাকে বাড়ীতে এসে প্রতিদিন চারটা মাছের তেলের ক্যাপসুল খাওয়াবে এবং এই ক্যাপসুল তিন মাস খেতে হবে। পরে একজন মাঠকর্মী আপনাকে এসে কিছু প্রশ্ন করবে এবং বাচ্চা জন্মানোর পরে বাচ্চার ওজন ও লম্বতা পরিমাপ করবে। আপনাকে একটা কার্ড দেয়া হবে এবং বাচ্চা জন্মানোর সঙ্গে সঙ্গে আপনার পরিবারের একজন সদস্য স্বাস্থ্যকর্মীকে তা জানাবে। একজন মাঠকর্মী এসে আপনার শিশুর ওজন ও লম্বতা পরিমাপ করবে।

আপনি এই গবেষণায় রাজী থাকলে নীচে স্বাক্ষর অথবা বৃদ্ধাঙ্গুলীর ছাপ দিন।

মাঠকর্মীর স্বাক্ষর

তারিখঃ

মায়ের স্বাক্ষর/বৃদ্ধাঙ্গুলির ছাপ

তারিখ ঃ

ABSTRACT SUMMARY FOR ERC

Title of the Study : **Efficacy of Fish-oil Supplementation to Pregnant Mothers on Birth Weights of their Babies.**

PROJECT SUMMARY:

The proportion of low birth weight (LBW) is very high in south Asia, and highest in Bangladesh with a proportion of 40-50%. LBW has increased risk of morbidity, mortality, diminished cognitive function, and increased chronic diseases in adulthood. Therefore, prevention of LBW has been identified as a high priority in south Asia. Several studies have shown beneficial effects of dietary intervention with macro and micronutrients to improve birth weights.

Previous studies conducted in Denmark showed that supplementing fish oil containing n-3 fatty acids (docosahexaenoic and eicosapentaenoic acids) to pregnant mothers significantly increased the birth weight of their newborns. A possible mechanism could be these fatty acids improve transplacental blood and nutrient supply, reduces intra uterine growth retardation.

We propose to conduct a double-blind randomized trial with supplementation of 4 g of fish oil (test) or 4 g olive oil (control) daily during the third trimester of pregnancy. This study will be carried out in Dhaka city with 400 pregnant women identified in the 25th week of gestation by community workers. These community workers will visit the pregnant women at home every day and will ensure compliance by direct supervision. Compliance will be checked by one of the investigators in 10% of cases by a random visit.

Trained nutritionists will be recruited as interviewers for data collection. Baseline data will include socioeconomic, anthropometric, and food intake data (24-h recall and food frequency). Each mother/infant pair will be visited within 24-h of delivery. The outcome variables are birth weight, length, head and chest circumferences of the new born babies. The proportion of LBW will be calculated and compared between the groups.

Results of this study will be useful for planning and implementing health intervention programs aimed at reducing the rate of LBW and improving child survival.

1. Four hundred pregnant mothers from Badda, a low socio-eco0nomic population will be studied. Low birth weight in Bangladesh is a major public health problem, particularly in lower SES. This study will help if Fish-oil supplementation improve birth weight.

2. Fish-oil is a food and this has been studied in developed country. No potential risk has been noted.

3. Not applicable.

4. No person other than investigators of the project and Ethical Review Committee will have access to the data generated in the proposed trial.

5. Informed consent will be obtained from the subjects.

6. Pregnant mothers will be interveiwed during the third trimester of the pregnancy to obtain some baseline information and after delivery which will be for 30 minutes.

7. If fish-oil supplementation helps to improve birth weight the subjects will have direct benefit and result of this study will be very important to reduce LBW in Bangladesh.

8. Patients records, body weight, height and babies body weight and length will be needed for data analysis.

Reviewer No 1

Title: The effect of fish-oil supplementation to pregnant mothers on low birth weight

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

	Rank Score		
	High	Medium	Low
Quality of project		✓	
Adequacy of project design		✓	
Suitability of methodology		✓	
Feasibility within time period	✓		
Appropriateness of budget			
Potential value of field of knowledge		✓	

CONCLUSIONS

I support the application:

a) without qualification / /

b) with qualification

- on technical grounds /✓/
- on level of financial support / /

I do not support the application / /

Name of Referee: Alan Ashworth FRCP

Signature: A. Ashworth Date: 3-8-38

Position: Professor of Community Medicine

Institution: London School of Hygiene & Tropical Medicine

ndon School of Hygiene & Tropical Medicine
ersity of London)

Bedford Square, London WC1B 3DP Tel: 0171 299 4600 Fax: 0171 436 5389
Direct Tel: 0171 299
Direct Fax: 0171 467 9529
e-mail: initial.surname@lshtm.ac.uk

Public Health Nutrition Unit
Department of Epidemiology and Population Health
Head: Professor P. Shetty

From: Self <EPSJ/EPHNAHIL>
To: musalam@icddrb.org
Subject: External Review (Dr Kabir)
Date sent: Mon, 9 Aug 1999 16:04:57

Dear Dr Salam

This proposal is an effectiveness study to examine whether fish oil supplementation in the third trimester of pregnancy reduces the incidence of LBW. As the authors correctly say, there have been few studies of fish oil supplementation and none in developing countries. The previous randomised trials (fish oil vs olive oil and fish oil vs placebo) were suggestive of an effect but not conclusive. The authors do not mention either of these previous trials, which would be considered a serious omission should this proposal be submitted for funding. Since an effect has not been established, it is more important scientifically to conduct a good efficacy trial at this stage than to undertake an effectiveness trial.

Problems with the RATIONALE:

Fish oil is said to prevent preterm births. This may be true but this mode of action is unlikely to be relevant in Bangladesh. The investigators therefore need to put forward a much more convincing case that fish oil also prevents IUGR. In the current proposal, various statements are made about the possible mode of action of fish oil in this respect, but these key references are not given.

If the proposal is to be submitted for funding, the text needs editing to remove incorrect statements and typgraphical errors. For example in the opening para, the sweeping statement about nutritional interventions being inconclusive is no longer correct (eg balanced protein/energy supplementation is now widely accepted as having a significant impact on BW in developing countries). Then in the third para the text incorrectly reads '25th month of gestation'. And in the opening para of the background, it incorrectly says that LBW indicates that an infant was malnourished in the womb (and thus disregards adequately-grown preterm infants).

Correct

Problems with the DESIGN and sample size:-

1. As mentioned above, considering the current state of knowledge, an efficacy trial would be preferred.

2. Both intervention and control groups are to be advised to eat more during the third trimester. This nutritional advice has the potential to increase BW independently from the fish oil. There are two problems here: a) the study will lose power as the sample size will be too small since both groups are likely to have a lower incidence of LBW

'than the population median of 40%. b) the counsellors are likely to differ in their effectiveness, so this advice may be implemented with varying impact, confounding any effect of fish oil. And the 24h recalls would not be sufficiently precise or accurate to help deal with this.

3. Another problem with sample size is the estimated magnitude of the effect. It is assumed that the incidence can be halved (from 40% to 20%) as a result of fish oil supplementation. There is no evidence in the literature as far as I am aware to suggest that such a huge impact is warranted. Smaller impacts, however, would still be of public health significance, if they were achievable.

4. It is proposed to measure mortality and morbidity during the first 7-10 days. The sample size is too small for this, and the exact time interval would have to be fixed (i.e. not a range). Nowhere are these outcomes mentioned as outcomes of interest.

5. It is not clear why the babies would all be measured again at 7-10 days plus a clinical examination when they have already been examined and measured within 72h of delivery. Improvement in size at birth is the outcome of interest and not their size at 7-10 days. Neither is their feeding status at 7-10 days relevant to the hypothesis.

6. Stratifying by parity could be unduly complicated. Since it is only first births who are smaller, then a separate random allocation could be used just for 'first births' and for 'others'.

7. It is not clear what value would be the baseline and monthly 24h recall and food frequency data. Is this to indicate if the groups are comparable in intakes of fatty fish and are not self-dosing with fish oil? If so, a few targeted questions would suffice.

Problems with the METHODOLOGY:

1. It is not clear what is proposed to be done with the 'measured bias' of the delayed BW measures. Is the plan to extrapolate back to an assumed BW at delivery? This is important if %LBW is the outcome, as a baby classed as 'LBW' at the time of measuring may not have been LBW at birth. But it is fraught with difficulty because the baby's weight measured many hours after delivery will also vary with feed time etc. and not just evaporative loss. Less of a problem would be mean BW as the outcome for comparison, as one would expect that both groups will be similar in infant age when first weighed.

2. For those born in hospital, it will not be acceptable to use the recorded hospital weights. The FWs must go and find these

babies too, and measure them in the same standard way as for all the others.

3. Measuring compliance is very difficult and cannot be relied upon by the method indicated. This is a further reason for having an efficacy trial so that actual consumption is supervised.

4) What will the investigators do if gestational age by LMP and Capurro disagree?

Problems with BUDGET.
There will be 50,000 capsules of fish oil needed and 50,000 olive oil. The budget ($9000) for these is insufficient.

Conclusion. Effective interventions to reduce the incidence of LBW in Bangladesh are a priority for improving public health. Fish oil supplementation trials have been undertaken in Denmark and the UK. The effects are modest and not significant. A good efficacy trial in a malnourished population would provide important insights as to whether fish oil has an effect or not. Once this is established, a decision can then be taken as to whether this is an intervention that is likely/unlikely to be beneficial. The present design has too many uncertainties to answer this question (uncertain compliance, uncertain/variable dietary advice).

I therefore support this proposal but with qualification on technical grounds.

I rank the proposal as follows:-

Quality	Medium
Design	Medium
Methods	Medium
Feasible	High
Budget	Inappropriately low
Value	Medium/Low

I will mail the summary sheet.
Yours sincerely
Ann Ashworth Hill

Reviewer # 2

Title: The Effect of Fish-oil Supplementation to Pregnant Mothers on Birth Weight of their Infants.

Summary of Referre'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 [X]

b) with qualification

- on technical grounds [ ]
- on level of financial support [ ]

I do not support the application [ ]

Name of Referee:

Signature: Date: 4 November 1999

Position:

Institution:

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: The effect of Fish-oil supplementation to pregnant mothers on birth weight of their infants

PI: AKM Iqbal Kabir et al

Reviewer:

To my knowledge no trial is currently available from developing countries testing the effect of fish oil in pregnancy. The proposed trial will thus contribute to filling in this gap.

It will be important that the results report separately the impact on IUGR and preterm birth. Current available evidence indicate a statistically significant reduction (of about 20%) in preterm birth rates with fish oil supplementation with narrow confidence intervals (see Villar J, Gülmezoglu M, de Onis M. Nutritional and antimicrobial interventions to prevent preterm birth: an overview of randomized controlled trials. **Obstetrical and Gynecological Survey** 1998;53:575-585).

Sample size in both arms of the trial should be increased if possible.

Compliance maybe a problem because of the fish oil unpleasant taste. Will the fish oil and olive oil capsules will be indistinguishable in taste too?

Precision and accuracy are assessed by TEM and bias, respectively.

Is not clear which method will be used for determining gestational age: LMP or Capurro? This needs to be decided in advance as these methods may yield different results.

It is mentioned that anthropometry will be taken within 72 hours of delivery. As birth weight and head circumference change considerably during this time period, it is important that the measurements are adjusted for time lag since birth. Specially, birth weight as one of the main outcome variables of the study.

In the logistic section it is mentioned that "arrangements will be made with clinics and hospitals for collecting information on birth weight". Birth weight is a key variable, thus, it needs to be collected by trained staff from the study following standardized procedures and using reliable measuring equipment. The birth weight from hospitals should not be used in the final analysis.

The reference de Onis, Villar, Gulmezoglu on "Nutritional interventions to prevent IUGR: evidence from randomized controlled trials" (Eur J Clin Nutr 1998;52:S1, S83- S93) , which is mentioned in the text of the proposal more than once, is not included in the reference list.

Responses to Reviewer 1.

The reviewer has correctly mentioned that there have been only few studies done in developed countries and none in developing countries where problem of LBW is very high. So there is a need to evaluate the efficacy of Fish-oil to reduce LBW in a developing countries.

Problems with rationale:

Although studies from Denmark have shown that the reduction of LBW may be due to reduction of preterm delivery, which may not have much relevance for Bangladesh. However, recent evidence suggests that birth weights were higher in Denmark and Sweden even after adjusting the gestational age (Ref. Olsen 1986; Lancet, Houwelingen 1995, Brit J Nutr, Villbergsson G 1991; Int J Gyn Obst). These results indicate that supplementation with fish-oil perhaps increased birth weight by not only preventing prematurity but also by improving transplacental nutrient supply.

Specific Questions.

1. Yes, a supervised efficacy trial will be carried out. The CWs will visit the pregnant women daily and will directly feed the fish-oil capsules.

2. The effectiveness of general recommendation to increase the food intake during pregnancy is not fully defined. There is no strong evidence that just giving dietary advice to increase intake will have a major impact. In a recently conducted operation research of BINP thana where additional 600 kcal has been provided daily to pregant women, but could not reduce the proportion of low birth weight (40-50%).

3. We agree that the sample size estimated with an expectation of reducing the LBW rate from 40% to 20% is ambitious. However, with the budgetary constrain and to have a efficacy type of trial to see if there is any reduction to around 25% as suggested by the reviewer would still be of public health significance. The sample size has been now recalculated to be 400 with an expected reduction of rate of LBW from 40% to 25%.

4. We agree with the reviewer about the comments regarding the mortality and morbidity and this will therefore, not be monitored.

5. As above there will not be any follow-up visit at 7-10 days.

6. This is a good suggestion and will be incorporated. However, we think the distribution of parity will be similar in both the groups. Adjustment may be done during analysis.

7. The baseline data and monthly 24h recall and food frequency will be used with regards to total energy intake, whether groups were comparable.

Problems with methodology:

1. We shall measure the babies body weight within 24 hours. Birth weight will also depend on evaporative loss, feeding status, however, randomization procedure is expected to result in equal distribution in both the groups.

2. We agree with this and Field Research Assistants (FRAs) will go and find these babies and will measure the babies in the hospitals and clinics in the same standard way as for all others.

3. We agree measuring the compliance is difficult, but we now propose to have Community Workers (CWs) visit each pregnant mother daily and provide capsules to ensure intake.

4. Only LMP will be used.

5. Yes, budget is insufficient but only this amount of fund was available. We shall try to get additional fund for fish-oil and olive oil capsules.

Responses to Reviewer 2.

1. The second reviewer has also correctly emphasized that although few studies have been done in developed countries with fish-oil supplementation to reduce the LBW, but none so far in developing countries where LBW is so high.

2. Yes, the impact of fish-oil supplementation on IUGR and preterm will analysed separately and reported accordingly.

3. Sample size has been increased. Reference has been incorporated.

4. We shall make the fish-oil and olive oil capsule indistinguishable in appearance, but I am not sure whether the taste can be the same. But the study will be randomized and only objective outcomes such as anthropometry will be measured.

5. To determine the gestational age only LMP will be used.

6. This is similar what the other reviewer has also mentioned. The field research assistants will measure the birth weight within 24 hours of delivery.

7. If the baby is delivered in the clinic or hospital the FRA will go and visit the hospital/clinic and will take anthropometry as the same way using standardized measurements. This has been incorporated in the protocol.

7. This reference has been quoted in the text but unfortunately not mentioned in the reference section. This has been now included in the reference section.