Attachment 1. REVISED Library Date 23/1/95.
(FACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Dr. M. Anwarul Islam

Principal Investigator Dr. Simon C LNG Trainee Investigator (if any)

Application No. 94 - 023 Supporting Agency (if Non-ICDDR,B) UNIVERSITY OF EDINBURGH,

Title of Study AN INVESTIGATION OF THE ROLE OF ZINC IN CATCH-UP GROWTH AMONG MALNOURISHED CHILDREN IN DHAKA, BANGLADESH.

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 N/A
   (d) Sensitive questions Yes No N/A
   (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 N/A
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:
   N/A Umbrella proposal - Initially submit 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)
   N/A Informed consent form for subjects-
   ✓ Informed consent form for parent or guardian
   N/A 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 summar
   1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
   2. Examples of the type of specific questions to be asked in the sensitive areas.
   3. An indication as to when the questionnaire will be presented to the Cttee. for review.

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

Principal Investigator Trainee

ENTERED 2 1 JUN 1998

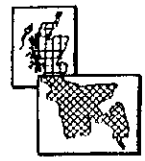
EdinburghDhakaLink **Catch-up Growth & Nutrition**

Research protocol

1.	**Title**	**An investigation of the role of zinc in catch-up growth among malnourished children in Dhaka, Bangladesh.**
2.	**Principle investigators**	Dr M Aminul Islam Dr Simon C Ling.
	Co-investigator	Ms Julianne P Ling Dr Dilip Mahalanabis Dr William AM Cutting.
3.	**Starting date**	As soon as approval is obtained.
4.	**Completion date**	26 months following start date.
5.	**Total direct costs**	US$ 34,275.00 (provisional)
6.	**Source of funding**	University of Edinburgh, UK.
7.	**Scientific division**	This protocol has been approved by the Clinical Sciences Division.

Signature of the Divisional Director, Clinical Sciences Division

Date: _____



EdinburghDhakaLink Catch-up Growth & Nutrition

An investigation of catch-up growth among malnourished children in Dhaka, Bangladesh.

Abstract

The rôle of zinc in improving catch-up growth in severely malnourished children will be examined with particular reference to linear growth, and the associated changes in various biochemical markers of growth and bone turnover, in a prospective, randomised, controlled trial.

195 children aged 6 to 24 months will be recruited from the Nutrition Rehabilitation Unit (NRU) of the ICDDR,B over a period of 18 months. They will be randomised to receive either 10mg / kg /day of zinc or a placebo suspension throughout their NRU admission and following discharge to day 30 after enrolment. Out patient follow-up will occur to day 90.

Measurements of weight, length, lower leg length, skin fold thickness and mid upper arm circumference will be made at intervals throughout the study. Lower leg length will be measured by portable knemometer. Nutritional intake during admission will be recorded. Foods offered will be randomly assayed for zinc content. Morbidity during follow-up will be documented, and feeding following discharge will be assessed by questionnaire. Other follow-up will be conducted as usual for children discharged from the NRU.

Blood and urine specimens will be collected on 3 occasions during each child's follow up and assayed for insulin-like growth factor-1 (IGF1), IGF binding protein 3 (IGFBP3), procollagen type 1 C terminal propeptide (P1CP), procollagen type 3 N terminal propeptide (P3NP), bone alkaline phosphatase, pyridinoline (PYD), and deoxypyridinoline (DPD).

Principal outcome variables will be change and rate of change of weight-for-age Z-score, height-for-age Z-score, weight-for-height Z-score, lower leg length for age, and of the biochemical markers listed above.

Reviews

1) **Chairman, Research Review Committee:** .....

2) **Chairman, Ethical Review Committee:** .....

3) **Director, ICDDR B** .....

An investigation of the role of zinc in catch-up growth among malnourished children in Dhaka, Bangladesh.

Project Proposal

Aims

The study is designed to answer the following questions:

i) Does zinc supplementation improve catch-up growth during refeeding of severely malnourished children?

ii) How do biochemical markers of growth and bone turnover relate to catch-up growth?

iii) How do these markers relate to the intake of zinc during catch-up growth?

Background

Severely malnourished children requiring treatment in a nutritional rehabilitation unit are at the extreme end of a spectrum of malnutrition found in many developing countries. Their survival depends on their ability to exhibit adequate catch-up growth, and this in turn is dependent on nutrition. The importance of other factors varies between each of these children, but for them all the primary requirement is the correct mixture of nutrients in adequate quantity.

In refeeding severely malnourished children, the relative importance of different dietary components has been debated for some time. There is accumulating evidence that various micronutrients are essential for maximal rates of catch-up to be attained. A deficiency of any one of these micronutrients may inhibit a rate-limiting step in the growth process, thus impairing the apparent growth response to macronutrients[1].

Although some work showed no effect of zinc in improving catch-up growth in malnourished children[2], many other studies show it has a beneficial rôle[3 4 5]. The effect of zinc supplementation on linear growth is less clear. The inability to demonstrate a positive effect on linear growth in studies concerning nutritional rehabilitation of severely malnourished children may in some cases be due to the short time-span over which growth was assessed, rendering measured increments in length too inaccurate. When children in a rural Bangladesh community were supplemented for a year, zinc was shown to have a demonstrable effect on linear growth over that time period[6]. Knemometry enables meaningful assessment of growth in lower leg length over short time periods, and therefore may help to determine whether zinc has an effect on linear growth during refeeding from severe malnutrition.

Although widespread in tissue and metallo-enzymes, zinc is an element without significant body stores, and a dietary deficiency will therefore rapidly lead to growth failure. Zinc supplements may improve appetite[7], hasten mucosal repair after diarrhoea[8], enhance the deposition of

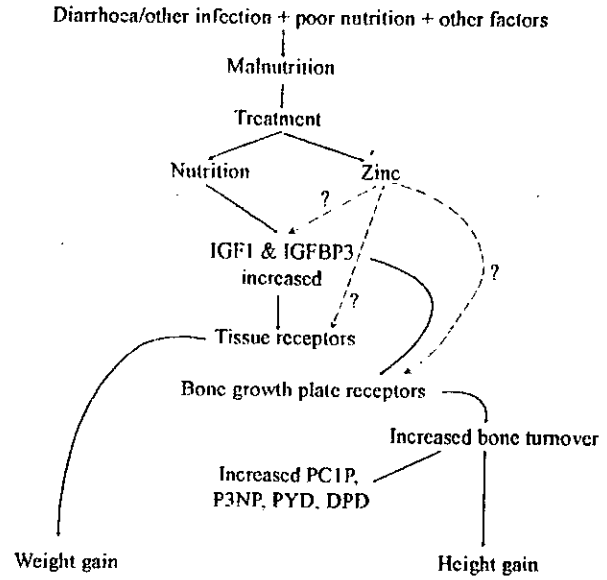
new lean tissue[9], and have a direct effect at the growth hormone and insulin-like growth factor 1 (IGF 1) receptors of malnourished children[10]. In the absence of an accurate measure of body zinc status, such children in Dhaka are thought to be zinc deficient because of the poor content of bio-available zinc in their diet[11] and the response many show to zinc supplementation[6 12]. Supplementing zinc intake during refeeding may therefore help to improve linear growth.

The mechanism and control of catch-up growth following malnutrition are not well described. A better understanding might enable a more focused approach to treatment. Pyridinoline and deoxypyridinoline are amino-acid cross-links of collagen that are excreted in urine when bone matrix is resorbed, and are therefore potential markers of bone turnover. They can be measured by reverse-phase high-pressure liquid chromatography[13 14]. They have been studied in the urine of severely malnourished children during nutritional rehabilitation, and their rate of excretion shown to be depressed during malnutrition and increased following catch-up[15]. The effect of zinc supplementation on these markers has not been studied.

In addition, other markers of bone and soft-tissue growth can now be measured in plasma. Bone alkaline phosphatase is a marker of osteoblastic activity during bone growth. Procollagen type 1 C terminal propeptide (P1CP) and procollagen type 3 N terminal propeptide (P3NP) are markers of, respectively, bone and soft tissue collagen formation[16]. They can be measured in plasma by radioimmunoassay[17 18]. Their relationship to growth of short normal children has been studied[19], but not to catch-up growth following malnutrition, nor to their response to zinc supplementation.

The concentration of insulin-like growth factor 1 (IGF1) in blood has been shown to be depressed in severely malnourished children and to rise following rehabilitation[20]. IGF binding protein 3 (IGFBP3) has been shown to be reduced in rats after prolonged fasting, and to increase after refeeding[21]. It has also been shown to be reduced in undernourished children with shigellosis, and to increase following refeeding[22]. These markers can be measured by radioimmunoasssay. Their relationship to length increments during refeeding of malnourished children has not been studied. Some work has suggested that zinc may have an independent influence on these markers, possibly through its rôle at the receptor level[10].

An outline of known and possible associations between growth, growth markers and nutrition is shown below:



We will undertake a randomised, prospective, controlled study following the anthropometric, knemometric, and dietary progress of severely malnourished children aged 6 to 24 months after admission to hospital. We will investigate the impact of an intervention involving zinc supplementation. We will also relate changes in biochemical markers of growth, bone and soft tissue turn-over to weight and length, total dietary intake and zinc intake.

Methods

Admission criteria

Children admitted to the Nutrition Rehabilitation Unit (NRU) of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) will be observed for 48 hours to exclude infection and then enrolled into the study according to the following criteria:

i) Weight for age less than 45% of the standard (current criterion for admission to the NRU)
ii) Age 6 to 24 months
iii) Informed consent obtained from parent(s).

Interventions

The ***zinc supplementation group*** will receive a daily supplement of 10 mg/kg elemental zinc as zinc acetate, mixed in a multi-vitamin syrup, starting on enrolment and continuing whilst in hospital and on discharge for a total of 1 month.

The ***placebo group*** will receive a placebo suspension of multi-vitamin syrup alone, identical in appearance and taste to the zinc supplement, and administered in the same way.

Randomisation

After enrolment into the study, children will undergo a stratified randomisation procedure. Stratification will be by age and type of malnutrition. Age strata of 6 - 9 months, 10 - 12 months, 13 - 18 months, and 19 - 24 months will be used. Two further strata will divide children into marasmus and marasmic kwashiorkor. Thus a total of eight strata will be generated.

Each stratum will have a randomly generated, serially numbered list detailing whether the next child in that stratum should receive a bottle of suspension containing zinc or placebo. The list will be generated and kept by an independent worker, who will subsequently make up all bottles at intervals throughout the study determined by the shelf life of the suspensions, and label them with the appropriate number. Study workers and subjects will remain blind to the contents of each bottle.

Follow up

Following entry to the study, background information will be collected by questionnaire, including family and socioeconomic details. Socioeconomic status will be assessed by direct measures, such as the occupation and salary of the parents, and indirect measures, such as house construction materials, water source, latrine availability, etc. These measures will be detailed individually, and also a 'socioeconomic score' will be constructed to reflect the overall status of the family using all the individual data. Details of the admission and illness preceding enrolment will be documented, including nature of illness (diarrhoea, pneumonia, etc), number of days with illness, type of diarrhoea (bloody or non-bloody), nature and duration of any treatment received prior to enrolment. Supplementation will commence according to randomisation.

Children will remain on the NRU for 15 days, and will then be seen as out-patients on days 21, 30, 45, 60, 75 and 90. The day 21 visit will be to reinforce the need to continue the supplement and to discuss any difficulties. All out-patient visits will involve measurements and questionnaires. Other activities at these follow-up visits will be identical to normal ICDDR procedure. Failure to attend an out-patient appointment within 3 days of the expected day will prompt a home visit to ensure follow-up is as complete as possible. Travel costs to and from the hospital will be reimbursed.

Sampling Blood and urine specimens will be collected on days 0, 15 and 30, and assayed for full blood count, IGF1, IGFBP3, PC1P, P3NP, PYD, DPD and bone alkaline phosphatase. Urine will be collected as a single specimen using an adhesive bag. All samples will be collected between 0800 and 1300 on each occasion, during which time minimal diurnal variation of the markers has been demonstrated (personal communication, B Golden). Separation and storage of specimens will occur at the ICDDR immediately after collection. Specimens will be stored frozen at -20^{0}C, and transported frozen to Edinburgh for analysis.

Measuring In order to assess the pattern of catch-up, which is unlikely to be linear, and unlikely to be the same for weight and length, frequent measurements will be taken. Knemometry will be carried out daily until discharge (allowing accurate analysis of the day-to-day variations to minimise errors due to interpretation of infrequent measurements), and then on days 21, 30, 45, 60, 75 and 90. Length will be measured on enrolment, and on days 15, 21, 30, 45, 60, 75 and 90. Weight will be measured daily until discharge, and then on days 21, 30, 45, 60, 75 and 90. Skin fold thicknesses and mid upper arm circumference will be measured on enrolment and days 15, 21, 30, 45, 60, 75 and 90. All measurements will be carried out by designated, trained staff members working solely on this research project. One of three staff members will perform knemometry, and the study will commence only once all three have attained a level of expertise necessary to produce accurate and reproducible measurements.

Nutrition Food intake during the NRU in-patient stage will be assessed using standard measures of each food offered. Frequency of breast feeds will be noted throughout the admission. During every alternate 24 hour period for each child, full assessment of breast milk intake by test weighing pre- and post-feed will be undertaken. Questionnaire information will be collected at each out-patient visit to determine the nature of foods being offered to the child at home.

Random sampling of foods offered during the NRU admission will occur and assay of zinc content performed by atomic absorption spectrophotometry at ICDDR. A day will be selected at random from every other month of the study. On that day, one child on the NRU in the study will be selected at random. At each meal time during that day, a sample of each food offered to that child will be collected and subjected to analysis for zinc content. Zinc breast milk concentrations in Bangladesh have been detailed previously[11] and found to be similar to other countries around the world. This will therefore not be assessed again.

Morbidity Evidence of intercurrent illnesses during admission will be detailed. Questionnaire information will be collected at each out-patient visit to determine occurrence of illness whilst at home. Mothers will be provided with a home-based chart suitable for use by illiterates to record episodes of diarrhoea and respiratory infections as they occur. Supplementation will continue to day 30 and all other follow-up will continue unchanged in case of intercurrent illnesses during the follow-up period.

Medical provision

Children under study will be referred for appropriate treatment of intercurrent illnesses. Mothers will be encouraged to present their children for immunisations if necessary.

Quality control

Measures will be taken to ensure, as far as practically possible, the accuracy of all measurements and the compliance of the study subjects. These are outlined below.

i) Freezer temperatures will be checked and recorded every morning and evening. Weighing scales, rollermeters, skin fold callipers, and knemometers will all be calibrated on a fortnightly basis, depending on the manufacturer's recommendations.

ii) The technique of Fellow Health Assistants and Project Supervisors in undertaking the measurements will be standardised initially and at 4 month intervals. Regular random checks for inter- and intra-observer error will be undertaken.

iii) Daily checks will ensure completeness of data during NRU admissions. Fellow Health Assistants will check the out patient data forms for completeness prior to the subject's departure, and these will be checked again at the end of the day by a project supervisor.

iv) Project supervisors will be available at all times for problems to be discussed, with additional weekly and two monthly meetings to discuss progress, feed back quality control results, and discuss methods for optimising performance.

v) Data will be double entered onto a computer by the project supervisors.

v) Unannounced duplicate specimens will be introduced into the laboratory system in addition to the standard laboratory quality controls.

Outcome measures

i) Change and rate of change of
- lower leg length,
- height for age Z-score,
- weight for age Z-score,
- weight for height Z-score,
- skin fold thickness, and
- mid upper arm circumference.

ii) Change and rate of change of
- IGF1,
- IGFBP3,
- PC1P,
- P3NP,
- PYD,
- DPD, and
- bone alkaline phosphatase

Statistics

Statistical advice has been taken from the Department of Medical Statistics, University of Edinburgh. Statistical analysis of the results will be performed in Edinburgh.

To assess whether zinc supplementation improves catch-up growth during refeeding of severely malnourished children, the mean changes in weight for age Z-score, height for age Z-score, weight for height Z-score and lower leg length for age over the full follow-up period will be calculated and compared in the two groups. Mean rate of change of these parameters in each group will be calculated for each week of in-patient stay and each interval of out-patient follow up and compared between groups. The effect of illness during the follow-up period will be assessed using change and rate of change data in children with and without illness during the follow-up period in each group. The possible rôle of other factors such as socio-economic status, feeding pattern at home, nature of illness before enrolment, etc will be assessed. Food intake during the in-patient stay will be compared with growth rates at the individual child level using correlation and multiple regression.

To assess how biochemical markers of growth and bone turnover relate to catch-up growth, values of each marker at each sampling time will be compared at the individual child level with growth rates as measured by the indices outlined above, using correlation and multiple regression. The pattern of change of markers during the catch up period will be examined.

To assess how the markers relate to the intake of zinc, the mean values of the markers at each sampling time in each group will be compared between groups. The intake of zinc from the refeeding diet will be estimated from intake data and food analysis data, and the similarity between groups compared. The estimated total intake of zinc during the NRU admission will be compared with the values of the markers at day 0 and day 15 at the individual child level using correlation and multiple regression. This comparison will also be performed controlling for mean protein and calorie intake for each group.

For the comparison of outcome in the two randomised groups, the choice between t-test or Wilcoxon test will depend on the distribution of the mean outcomes.

Associations between different outcomes and between outcomes and demographic factors will be assessed within each treatment group separately at the individual child level using correlation and multiple regression.

Groups will be compared to ensure similarity in sex and age distribution, socioeconomic status, feeding practices, and detail of illness preceding admission to the NRU.

Sample size

With 90% power at the 5% level, the following approximate sample sizes would be required (formula $n = 10.5 (SD_1^2 + SD_2^2) / D^2$ where SD_1 and SD_2 are the standard deviations in control and intervention groups, and D is the difference in the outcome measure between the two groups.)

i) Bisgaard *et al*[23] showed the SD of normal lower leg length in this age group to be 153 µm / day, and the daily leg length growth using weekly measurements to be 92 µm / day. Using these figures in the above formula, to show a difference between the groups of 92 µm / day increase in lower leg length, **n = 29**. The accuracy of measurements with the portable knemometer is approximately 50 µm / day.

ii) Kabir *et al*[24] showed a difference in change of height for age Z-score of 0.09 between groups fed normal protein or high protein diet in malnutrition refeeding. Standard deviations of the two groups were 0.04 and 0.12. Using these figures, in order to show a

difference of 0.09 in change of height for age Z-score between the two intervention groups, **n = 21**.

iii) Kabir *et al*[24] showed a difference in change of weight for age Z-score over 21 days of 0.23 between groups fed normal protein or high protein diet in malnutrition refeeding. Standard deviations of the two groups were 0.27 and 0.38. Using these figures, in order to show a difference of 0.23 in change of weight for age Z-score between groups, **n = 43**.

iv) Kabir *et al*[24] showed a difference in change of weight for height Z-score over 21 days of 0.25 between groups fed normal protein or high protein diet in malnutrition refeeding. Standard deviations of the two groups were 0.4 and 0.46. Using these figures, in order to show a difference in weight for height Z-score of 0.25 between groups, **n = 62**.

v) Skin fold thickness and mid upper arm circumference - data for calculation of sample size not available.

vi) Kabir *et al*[25] showed a difference of 23.4 nmol / l in change of IGF 1 following refeeding malnourished children with normal protein *vs* high protein diet. Standard deviations in the two groups were 16.2 nmol / l and 9.2 nmol / l. Using these figures, in order to show a difference of 23.4 nmol / l in change of IGF1 between groups, **n = 7**.

vii) IGF BP3 - no data available for sample size calculations.

viii) Trivedi *et al*[16] showed a difference in P1CP levels of 130 µg / l between children with average height velocity of 2.18 cm / y and 6.02 cm / y. Standard deviations in the two groups were approximately 250 µg / l. Using these data, in order to show a difference of 130 µg / l in change of P1CP between groups, **n = 39**.

ix) Trivedi *et al*[16] showed a difference in P3NP level of 2.1 µg / l between children with average height velocity of 2.18 cm / y and 6.02 cm / y. Standard deviations in the two groups were approximately 4.125 µg / l. Using these data, in order to show a difference of 2.1 µg / l in change of P3NP between groups, **n = 41**.

x) Branca *et al*[15] showed a difference in PYD of 21 nmol / h / m^2 between malnourished and recovered children. Standard deviations of the two groups were 4.6 nmol / h / m^2 and 10.8 nmol / h / m^2. Using these data, in order to show a difference of 5 nmol / h / m^2 in change of PYD between groups, **n = 58**.

xi) Branca *et al*[15] showed a difference of 4.9 nmol / h / m^2 in DPD between malnourished and recovered children. Standard deviations of the two groups were 1.3 nmol / h / m^2 and 3.0 nmol / h / m^2. Using these figures, in order to show a difference of 2.5 nmol / h / m^2in change of DPD, **n = 18**.

Taking the largest of these sample size calculations, the total sample size would need to be 124.

In-patient statistics of the ICDDR NRU suggest a recruitment rate to the study of approximately 2.5 patients per week, giving a total sample size of 195 subjects if recruitment continues for 18 months. Allowing for 20% drop out, complete data should be available on 156 subjects. This allows a 20% correction for confounding factors. Stratified randomisation should ensure that other confounding variables are equally represented in both intervention and control groups, although collection of data on socioeconomic status and morbidity during follow-up will enable these variables to be controlled for in a multiple regression analysis if necessary.

Ethical considerations

The project has been approved by the Paediatrics and Reproductive Medicine Research Ethics Sub-Committee of Lothian Health, Edinburgh. Approval will also be sought from the Research Review Committee and Ethical Review Committee of the ICDDR,B.

Enrolment will occur only after the child's parent(s) have agreed with and signed a consent form. The parent(s) may withdraw their child from the study at any time following enrolment.

The study will involve 5 ml of venous blood being taken from each child on three occasions. These blood tests are essential to identify the response of the children to the intervention. In

order to elicit the pattern of response of growth and bone turnover markers, specimens are required at the start of catch-up, after some weight gain, and when catch-up is well established; three specimens are therefore required. Previous studies examining changes in IGF1, IGFBP3, PYD and DPD have used two samples only, one immediately related to an infection and the other a variable time later when catch-up was assumed to be continuing. Some of these markers are known to be depressed during an acute illness independent of the individual's growth rate. By taking three specimens, such an effect will be identifiable, the pattern of change of these markers during catch-up will be described, and the timing of at least one sample during active catch-up will be certain.

A recognised zinc preparation will be used (currently under negotiation). Zinc has been used in this dosage widely among the population being studied and others like it elsewhere without ill effect. Rarely, gastrointestinal disurbance may occur, and this will prompt withdrawal of the patient from the study.

Usual NRU treatment and follow-up procedures will continue as normal for the study children.

Personnel

A Bangladeshi project supervisor (Dr M Aminul Islam) will be joined by one full-time (Dr Simon C Ling) and one part-time (Mrs Julianne P Ling) project supervisor from the UK. Dr M Aminul Islam will assist in designing and writing the project protocol, undertaking knemometry and skin fold thickness measurements, and in writing the final reports and publications. Dr Simon C Ling will design and write the project protocol, undertake knemometry and skin fold thickness measurements, supervise the daily activities of the project staff, enter data onto a microcomputer, and write the final report and publications. Mrs Julianne P Ling will undertake knemometry and skin fold thickness measurements, assist in supervision of the daily activities of the project staff, and enter data onto a microcomputer. Dr Dilip Mahalanabis and Dr William AM Cutting will advise during project design, results analysis, interpretation and writing -up. Other staff detailed below will be recruited according to previous practice at the ICDDR.

Three 'Fellow Health Assistants' (graduates in Home Economics) will be employed to undertake measurements, document nutritional intakes, provide information to mothers, and perform home visits where necessary.

Four 'Health Workers' (minimal formal education, but training provided for the project) will endeavour to build a close rapport with the mothers, increasing their confidence in the project and maximising compliance. They will accompany a Fellow Health Assistant on home visits. They will observe mothers and children throughout their breast milk intake assessment periods.

One 'Trainee Physician' will also be employed to assist in the management of the study cases on the NRU and during out-patient follow-up.

References

1. Golden MHN. The nature of nutritional deficiency in relation to growth failure and poverty. Acta Paediatr Scand 1991;**Suppl 374**:95-110.
2. Hemalatha P, Bhaskaram P, Khan MM. Role of zinc in the rehabilitation of severely malnourished children. Eur J Clin Nutr 1993;47:395-399.

3. Khanum S, Alam AN, Anwar I, Akbar Ali M, Rahaman MM. Effect of zinc supplementation on the dietary intake and weight gain of Bangladeshi children recovering from protein-energy malnutrition. Eur J Clin Nutr 1988;**42**:709-714.

4. Castillo-Duran C, Heresi G, Fisberg M, Uauy R. Controlled trial of zinc supplementation during recovery from malnutrition: effects on growth and immune function. Am J Clin Nutr 1987;**45**:602-8.

5. Golden MHN, Golden BE. Effect of zinc supplementation on the dietary intake, rate of weight gain, and energy cost of tissue deposition in children recovering from severe malnutrition. Am J Clin Nutr 1981;**34**:900-908.

6. Sella GE, Talukder MQ-K, Das DK, Khan AH. Growth and morbidity in zinc-supplemented and non-supplemented infants in rural Bangladesh. In: McNeish AS, Mittal SK, Walker Smith JA, eds. Recent trends in diarrhoea and malnutrition. New Delhi: Dr S.K. Mittal, Second Commonwealth Conference on Diarrhoea and Malnutrition, 1991:189-197.

7. Krebs NF, Hambidge KM, Walravens PA. Increased food intake of young children receiving a zinc supplement. Am J Dis Child 1984;**138**:270-273.

8. Roy SK, Haider R, Tomkins A, Behrens RH. Effect of zinc supplementation on intestinal permeability and morbidity among Bangladeshi children with persistent diarrhoea syndrome. Proc Nutr Soc 1991;**50**:60A.

9. Golden BE, Golden MHN. Effect of zinc on lean tissue synthesis during recovery from malnutrition. Eur J Clin Nutr 1994;**46**:697-706.

10. Payne-Robinson HM, Golden MHN, Golden BE, Simeon DT. The zinc sandwich and growth. Lancet 1991;**337**:925-926.

11. Simmer K, Ahmed S, Carlsson L, Thompson RPH. Breast milk zinc and copper concentrations in Bangladesh. Brit J Nutr 1990;**63**:91-96.

12. Behrens RH, Tomkins AM, Roy SK. Zinc supplementation during diarrhoea, a fortification against malnutrition? Lancet 1990;**336**:442-443.

13. Robins SP, Black D, Paterson CR, Reid DM, Duncan A, Seibel MJ. Evaluation of urinary hydroxypyridinium crosslink measurements as resorption markers in metabolic bone diseases. Eur J Clin Invest 1991;**21**:310-315.

14. Black D, Duncan A, Robins SP. Quantitative analysis of the pyridinium crosslinks of collagen. Anal Biochem 1988;**169**:197-203.

15. Branca F, Robins SP, Ferro-Luzzi A, Golden M. Bone turnover in malnourished children. Lancet 1992;**340**:1493-1496.

16. Trivedi P, Ristelli J, Ristelli L, Hindmarsh PC, Brook CGD, Mowat AP. Serum concentration of type I and type III procollagen propeptides as biochemical markers of growth velocity in healthy infants and children and in children with growth disorders. Pediatr Res 1991;**30**:276-280.

17. Melkko J, Niemi S, Risteli L, Risteli J. Radioimmunoassay of the carboxyterminal propeptide of human type I procollagen. Clin Chem 1990;**36**:1328-1332.

18. Niemelä O. Radioimmunoassays for Type III procollagen amino-terminal peptides in humans. Clin Chem 1985;**31**:1301-1304.

19. Crofton PM, Schönau E, Stirling HF, Kelnar CJH. Can biochemical markers predict response to growth promoting treatment in short normal children? Pediatr Res 1993(Suppl);**33**:S35.

20. Hintz RL, Suskind R, Amatayakul K, Thanangkul O, Olson R. Plasma somatomedin and growth hormone values in children with protein-calorie malnutrition. J Pediatr 1978;**92**:153-156.

21. Clemmons DR, Thissen JP, Maes M, Ketelsegers JM, Underwood LE. Insulin-like growth factor-1 (IGF-1) infusion into hypophysectomised or protein-deprived rats induces specific IGF binding proteins in serum. Endocrinology 1989;**125**:2967-2972.

22. Pucilowska JB, Davenport ML, Kabir I, Clemmons DR, Thissen J-P, Butler T, Underwood LE. The effect of dietary supplementation on insulin-like growth factors (IGFs) and IGF-binding proteins in children with shigellosis. J Clin Endocrinol Metab 1993;**77**:1516-1521.

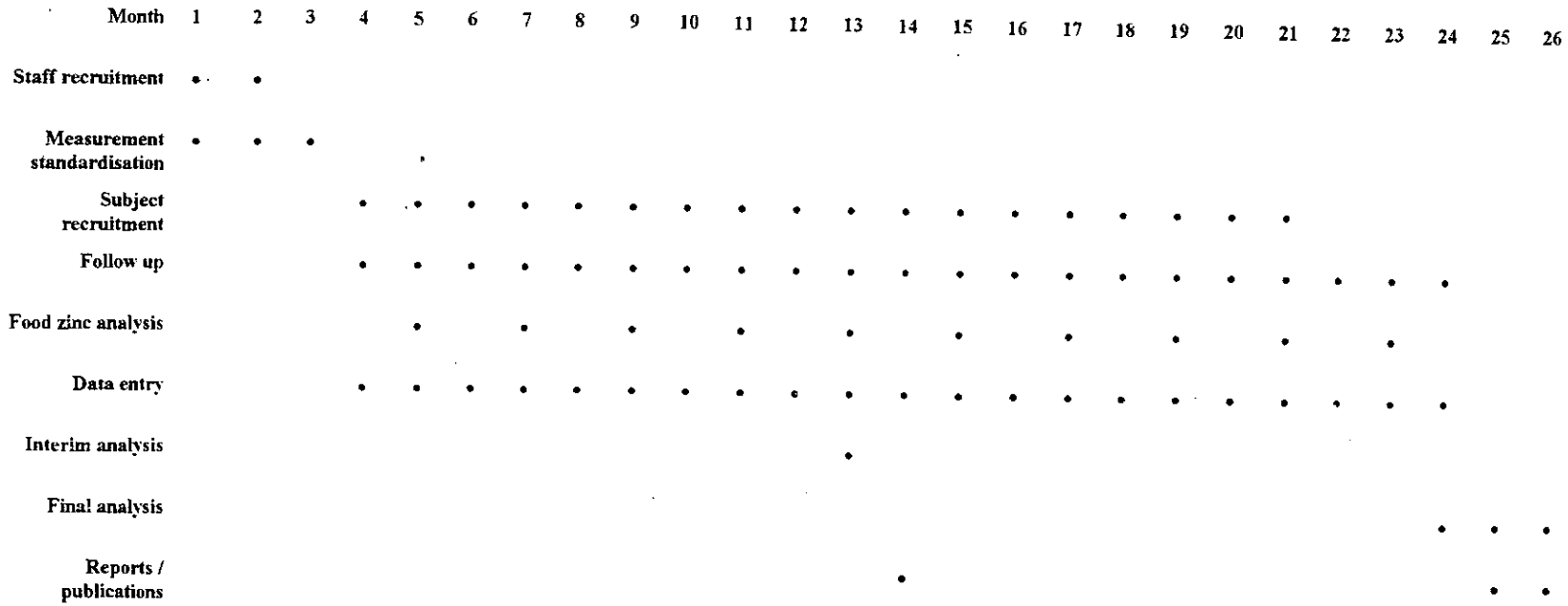
23. Bisgaard H. Systemic activity of inhaled topical steroid in toddlers studied by knemometry. Acta Paediatr 1993;**82**:1066-1071.

24. Kabir I, Malek MA, Mazumder RN, Rahman MM, Mahalanabis D. Rapid catch-up growth of children fed a high-protein diet during convalescence from shigellosis. Am J Clin Nutr 1993;**57**:441-445.

25. Kabir I, Butler T, Underwood LE, Rahman MM. Effects of a protein-rich diet during convalescence from shigellosis on catch-up growth, serum proteins, and insulin-like growth factor-1. Pediatr Res 1992;**32**:689-692.

An investigation of catch-up growth among malnourished children in Dhaka, Bangladesh.

Work schedule



Study number |__|__|__|

Edinburgh/Dhaka Link **Catch-up growth and nutrition**

Background data questionnaire

Name _____ **Date of Birth** |__|__| / |__|__| / |__|__|

Sex **M / F** **Date of NRU admission** |__|__| / |__|__| / |__|__|

Number |__|__|__| **Today's date** |__|__| / |__|__| / |__|__|

From general ward notes

1. Date of admission to the general ward |__|__| / |__|__| / |__|__|
2. What type of diarrhoea did the child have on the general ward? |__|
   (1) acute watery diarrhoea (2) acute invasive diarrhoea (3) persistent diarrhoea (4) none (5) other (specify). .....
3. Did the child have pneumonia on the general ward? *(1) yes (2) no* |__|
   (diagnosis proven by positive X ray)
4. What was the duration of diarrhoea prior to admission to general ward? *(days)* |__|
5. Was there clinical evidence of septicaemia? *(1) yes (2) no* |__|
   (diagnosis by unexplained lethargy, fever, +/- positive blood culture)
6. What was the child's weight on admission to the general ward? *(kg)* |__|__| . |__|__|
7. Which of the treatments below did the child receive on the general ward?
   - Ampicillin *(1) yes (2) no* |__|
   - Gentamicin *(1) yes (2) no* |__|
   - Cephalosporin *(1) yes (2) no* |__|
   - Erythromycin *(1) yes (2) no* |__|
   - Ciprofloxacin *(1) yes (2) no* |__|
   - Other antibiotic *(1) yes (2) no (specify)* ..... |__|
   - Iron *(1) yes (2) no* |__|
   - Folic acid *(1) yes (2) no* |__|
   - Zinc *(1) yes (2) no* |__|
   - Other treatment *(1) yes (2) no (specify)* ..... |__|

From mother or the general ward notes

Family background

8. How old is the child's mother? *(years)* |__|__|
9. How many year's education has she had? |__|__|
10. Does she work outside the home? *(1) yes (2) no* |__|
11. How many brothers (alive) does the child have? |__|
12. How many sisters (alive) does the child have? |__|
13. Does the child's father support the family? *(1) yes (2) no* |__|
14. What is his occupation? *(specify)* .....

Socio-economic background

15. What is the family's income in 1 month? *(Taka)* |__|
16. How many rooms does the child's house have? |__|__|
17. How many people live in the child's house? |__|__|
18. What is the house's roof made from? |__|
    (1) bamboo (2) thatched (3) corrugated tin (4) pacca

19. What is the house's floor made from? |__|
(1) earthen (2) pacca

20. Does the house have electricity? *(1) yes (2) no* |__|

21. What cooking fuel is used in the house? |__|
(1) cow dung (2) firewood (3) kerosene (4) gas

22. How much house rent does the family pay in 1 month? *(Taka)* |__|

23. Where does the family's drinking water come from? |__|
(1) surface water (2) pond (3) river (4) earthen well (5) ringwell (6) tubewell (7) standpipe

24. Where does the family's washing water come from? |__|
(1) surface water (2) pond (3) river (4) earthen well (5) ringwell (6) tubewell (7) standpipe

25. What toilet facilities does the family have? |__|
(1) none (2) open pit latrine (3) water seal latrine

26. Is the latrine shared? *(1) yes (2) no* |__|

27. Where does the family dispose of its garbage? |__|
(1) no fixed place (2) ditch (3) courtyard (4) dustbin
(5) other (specify) .....

Child's feeding pattern

28. Is the child still breast fed? *(1) yes (2) no* |__|

29. If no, how old was the child when breast feeding stopped? *(years and months)* |__|y|__||__|m

30. Was the child receiving milk other than breast milk before admission to the general ward? |__|
(1) yes (2) no

31. Did the child receive foods other than milk before admission to the general ward?
(specify foods) .....
.....
.....

Study number |__|__|__|

EdinburghDhakaLink **Catch-up growth and nutrition**

Follow-up data questionnaire

Name _____ **Date of Birth** |__|__| / |__|__| / |__|__|

Sex **M / F** **Date of NRU admission** |__|__| / |__|__| / |__|__|

Study number |__|__|__| **Today's date** |__|__| / |__|__| / |__|__|

History of illness

(Use the record sheet kept by the child's mother to help when filling in this section)

1. Since we last saw the child, has he / she been ill? *(1) yes (2) no* |__|
2. If yes, what illness has the child had? |__|
   (1) watery diarrhoea (2) bloody diarrhoea (3) cough with fast breathing
   (4) other illness (specify).....
3. On which day did the illness start? *(give date)*.....
4. On which day did the illness stop *(give date or state if still present)*.....

Feeding history

Over the last week, on how many days has the child received each of the foods below?

5. Breast milk |__|
6. Other milk |__|
7. Khichuri |__|
8. Halwa |__|
9. Green leafy vegetables, pumpkin or papaya |__|
10. Meat, fish, eggs, or liver |__|
11. Pulses |__|
12. Rice |__|

Measurements

13. Weight *(kg)* |__|__| . |__|__|
14. Length *(cm)* |__|__| . |__|
15. Lower leg length *(mm)* |__|__| . |__|__|
16. Triceps SFT *(mm)* |__|__|
17. Subscapular SFT *(mm)* |__|__|
18. MUAC *(cm)* |__|__| . |__|
19. Presence of oedema *(1) yes (2) no* |__|

BUDGET PROPOSAL

PROJECT TITLE : An investigation of catch-up growth ... Dhaka, Bangladesh

NAME OF DONOR : Univ. of Edinburgh

STARTING DATE :

PROJECT DURATION : 2 years from starting

CLOSING DATE :

NAME OF P. I. : Dr M. Amirul Islam & Dr Simon Ling

RPC APPROVAL DATE :

EPC APPROVAL DATE :

Amount in US Dollar

Line Item	Year		TOTAL
	1st year	2nd year	US$
	A	B	C=A+B
PERSONNEL LOCAL: SALARIES			0
Dr M. Aminul Islam, PI (10%)	1,176	1,200	2,376
Health Asstt. (CSA) - 3 x 24 m	2,700	2,700	5,400
Health Worker x 4 x 24 m	1,798	1,798	3,596
Fellow Doctor x 24 m	1,798	1,798	3,596
Sub-total:	7,472	7,496	14,968
TRAVEL (patient transportation cost)	800	363	1,163
Sub-total:	800	363	1,163
SUPPLIES & MATERIALS			
-Office Supplies	1,000	550	1,550
-Others	2,000	1,100	3,100
Sub-Total	3,000	1,650	4,650
OTHER CONTRACTUALS			
- Fax, phone, postage etc.	1,000	550	
- Publication	200	420	
Sub-total	1,200	970	2,170
INTER DEPARETMENTAL SERVICES			
-Transport; Land & Water	500	275	775
-Lab. and Pathological test	800	475	1,275
-etc			
Sub-Total	1,300	750	2,050
CAPITAL EXPENDITURE: Equipment, Furniture etc	1,163	0	1,163
			0
Sub-Total	1,163	0	1,163
TOTAL OPERATING COST	14,935	11,229	26,164
OVERHEAD @31%	4,630	3,481	8,111
TOTAL PROJECT COST	19,565	14,710	34,275

AHPO-B/BGFORMET.WK1

10/12/94

EdinburghDhakaLink **Catch-up Growth & Nutrition**

An investigation of catch-up growth among malnourished children in Dhaka, Bangladesh.

Consent form

Your child has been admitted to this unit because he/she is extremely thin. He/she needs to be carefully fed for two weeks or more to make him/her better. We are doing a study to help to find out what is best for a child to be fed at this important time, and how this might make him/her grow.

In the study, we will give some children a multivitamin syrup containing zinc, and others a multivitamin syrup without zinc. The children that get the zinc will be decided by chance. We will then see you during the admission here, and afterwards in the clinic every 2 weeks for 3 months, to measure your child. Some people have shown that zinc may improve the way a child grows, while others have not shown this. Zinc does not harm your child. By comparing the growth of children who get zinc with those who do not, we hope to show whether or not zinc helps.

We also want to look at how children grow after being sick. To do this we need to do three blood tests over a 1 month period. These blood tests involve one prick with a needle each, and a small amount of blood being taken for some tests to be done in the laboratory. The blood is taken from a vein, and each time we will take about 1 teaspoon-full (5ml). The tests will give us important information about how the zinc might work. We can give you more information about these tests if you want.

The study involves no risk to your child. There will be some minor, temporary discomfort due to the blood tests.

If you agree, we will include your child in the study. If you do not agree, then your child will still get all the normal treatment on the unit. If you agree now, but later change your mind, then you can remove your child from the study immediately without affecting his/her further treatment in this unit.

If you are happy for your child to be included in the study, please give your consent by signing this form.

If you have any questions about the study please ask.

Parent's / guardian's signature / left thumb print .....

Investigator's signature .....

Witness's signature .....

সম্মতি পত্র

"অপুষ্ট বাচ্চাদের স্বাস্থ্য বৃদ্ধিতে জিংকের ভূমিকা"

আই, সি, ডি, ডি, আর, বি

আপনার বাচ্চা অপুষ্ট বলে আমাদের এখানে ভর্তি করা হয়েছে। তাকে আমরা এই ওয়ার্ডে ২ সপ্তাহ বা বেশী সময় রেখে খাওয়াবো ও অন্যান্য চিকিৎসা করব। এই গবেষণায় আমরা দেখতে চাচ্ছি অপুষ্ট বাচ্চাকে কি খাওয়ালে তার স্বাস্থ্য বৃদ্ধি পাবে এবং সুস্থ হয়ে উঠবে।

এখানে থাকাকালীন আমরা প্রত্যেক বাচ্চাকে ভিটামিন ওষুধ দেব এবং অর্ধেককে সেই সাথে জিংক সিরাপ দেব। কে জিংক পাবে তা লটারী করে ঠিক করা হবে। এখানে ভর্তি থাকা অবস্থায় প্রতিদিন এবং ছুটির পর ১৫ দিন পর পর ৩ মাস পর্যন্ত বাচ্চার ওজন ও অন্যান্য মাপ নিয়ে দেখা হবে বাচ্চার উন্নতি হচ্ছে কিনা? ইতিপূর্বে গবেষণায় কেউ কেউ জিংক দিয়ে উপকার পেয়েছেন, কেউ কেউ পাননি। জিংক দিলে বাচ্চার কোন ক্ষতি হয় না। এই গবেষণায় আমরা জানতে পারব, জিংক দিলে স্বাস্থ্যের উন্নতি হয় কিনা।

আমরা আরো দেখব, অসুস্থতার পর আপনার বাচ্চার স্বাস্থ্য বৃদ্ধি হয় কিনা। এজন্য বাচ্চাকে প্রথম সপ্তাহে আমরা তিনবার রক্ত পরীক্ষা করব। প্রতিবারে শিরা থেকে প্রায় এক চা-চামচ (৫ মি.লি.) পরিমাণ রক্ত নেয়া হবে। এই রক্ত পরীক্ষায় আমরা জানতে পারব জিংকের কার্যকারীতা সম্পর্কে। এই পরীক্ষার ব্যাপারে আরো কিছু জানতে চাইলে আমাদেরকে জিজ্ঞেস করতে পারেন। এই অল্প পরিমাণ রক্ত নেয়াতে বাচ্চার কোন ক্ষতি হবে না। শুধুমাত্র রক্ত নেয়ার সময় বাচ্চার সাময়িক অস্বস্তি হতে পারে।

আপনি রাজী থাকলে আমরা আপনার বাচ্চাকে এই গবেষণায় নেব। আপনি রাজী না হলেও এই ওয়ার্ডের স্বাভাবিক চিকিৎসা আপনার বাচ্চাকে দেয়া হবে। আপনি যেকোন সময় গবেষণা থেকে আপনার সম্মতি প্রত্যাহার করে নিতে পারেন। তাতে এই ওয়ার্ডের পরবর্তী চিকিৎসার কোন ব্যাঘাত ঘটবে না। আপনার আরো কিছু জানার থাকলে আমাদের জিজ্ঞাসা করতে পারেন।

আপনি এই গবেষণায় আপনার বাচ্চাকে রাখতে চাইলে নীচের খালি জায়গায় আপনার স্বাক্ষর বা টিপসই দিন।

তারিখ	অভিভাবকের স্বাক্ষর / বাম বৃদ্ধাঙ্গুলির টিপসই
গবেষণাকারীর স্বাক্ষর	স্বাক্ষীর স্বাক্ষর