International Centre for Diarrhoeal Disease Research, Bangladesh
CENTRE FOR HEALTH AND POPULATION RESEARCH
Mail : ICDDR, B, GPO Box 128, Dhaka-1000, Bangladesh
Phone: 880-2-8811751-60, Telex : 642486 ICDD BJ
Fax : 880-2-8823116, 8812530, 8811568, 8826050, 9885657, 8811686, 8812529
Cable : Cholera Dhaka

Memorandum

5 March 2003

CSD
2002

To : Dr. Hasan Ashraf
Principal Investigator of protocol # 2002-036
Clinical Sciences Division

From: Professor Mahmudur Rahman
Chairman, Ethical Review Committee (ERC)

Sub : Approval of research protocol # 2002-036

Thank you for your memo dated 4th March 2003 with the modified version of your research protocol # 2002-036 titled "Daycare-based management of severe pneumonia in under 5 children when hospitalization is not possible due to the lack of beds". The modified version of the protocol is hereby approved upon your satisfactory addressing of the issues raised by the ERC in its meeting held on 26th February 2003.

You shall conduct the study in accordance with the ERC-approved protocol; and shall be responsible for protecting the rights and welfare of the subjects and compliance with the applicable provisions of ERC Guidelines. You shall also submit report(s) as required under ERC Guidelines. Relevant excerpt of ERC Guidelines and '*Annual/Completion Report for Research Protocol involving Human Subjects*' are attached for your information and guidance.

Thank you and I wish you all success in running the above-mentioned study.

Copy: Acting Associate Director
Clinical Sciences Division

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Memorandum

To: Professor Mahmudur Rahman
Chairman, Ethical Review Committee (ERC)

From: Dr. Hasan Ashraf
Principal Investigator of protocol # 2002-036
Clinical Sciences Division

Date: 4 March 2003

Sub: Approval of research protocol # 2002-036

Thank you very much for considering the modified version of my research protocol #2002-036 entitled "Daycare-based management of severe pneumonia in under 5 children when hospitalization is not possible due to the lack of beds" in the ERC meeting held on 26th February 2003.

I have replied to the comments in chronological order that is attached herewith. I am forwarding herewith the modified version of the protocol for your approval.

Thank you.

Enc: a/a

ERC Response (Protocol # 2002-036)

a) On the ERC Face Sheet, item # 4(d) should be marked 'YES' instead of 'no'.

Response: On the ERC Face Sheet, item # 4(d) has been marked 'YES' instead of 'no'.

b) Specific Aim # 2 should be dropped since it cannot be attained, as the cases admitted to hospitals and those to be treated at the Day Care Centre may not be comparable.

Response: Specific Aim # 2 has been dropped from the protocol (page 6).

Attachment 1 Date: 4 March, 2003

(FACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator: Dr. Hasan Ashraf

Application No. 2002—036

Title of Study: Daycare-based management of severe pneumonia in under 5 children when hospitalization is not possible due to the lack of beds

Trainee Investigator (if any): _____

Supporting Agency (if Non-ICDDR,B) _____

Project Status: _____

[√] New Study

[ ] Continuation with change

[ ] No change (do not fill out rest of the form)

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

1. Source of Population:
   - (a) Ill subjects — Yes
   - (b) Non-ill subjects — No
   - (c) Minor or persons under guardianship — Yes

2. Does the Study Involve:
   - (a) Physical risk to the subjects — No
   - (b) Social risk — No
   - (c) Psychological risks to subjects — No
   - (d) Discomfort to subjects — No
   - (e) Invasion of privacy — No
   - (f) Disclosure of information damaging to subject or others — No

3. Does the Study Involve:
   - (a) Use of records (hospital, medical, death or other) — Yes
   - (b) Use of fetal tissue or abortus — No
   - (c) Use of organs or body fluids — No

4. Are Subjects Clearly Informed About:
   - (a) Nature and purposes of the study — Yes
   - (b) Procedures to be followed including alternatives used — Yes
   - (c) Physical risk — Yes
   - (d) Sensitive questions — Yes
   - (e) Benefits to be derived — Yes
   - (f) Right to refuse to participate or to withdraw from study — Yes
   - (g) Confidential handling of data — Yes
   - (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — Yes

5. Will Signed Consent Form be Required:
   - (a) From subjects — No
   - (b) From parents or guardian (if subjects are minor) — Yes

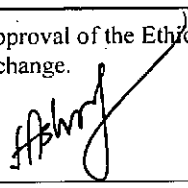
6. Will precautions be taken to protect anonymity of subjects — Yes

7. Check documents being submitted herewith to Committee:
   - NA 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
   - NA Informed consent form for subjects
   - √ Informed consent form for parent or guardian
   - √ Procedure for maintaining confidentiality
   - NA 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

ABSTRACT SUMMARY FOR ERC

Pneumonia is an infection of the lungs, most commonly caused by viruses or bacteria; however, most serious episodes in children are generally caused by bacteria, and *Streptococcus pneumoniae* and *Haemophilus influenzae* are the two most important among them. Depending on clinical presentation, pneumonia can be classified as very severe, severe, or non-severe, with specific treatment for each of them except for antibiotic therapy, which is indicated irrespective of the severity. Severe and very severe pneumonia require hospitalization for additional supportive treatment like suction, oxygen therapy, bronchodilator, nebulizer etc. In Bangladesh, the number of hospital beds are inadequate for admission of all pneumonia cases that require hospitalization. Provision of broad spectrum antibiotics, appropriate supportive care during the period of stay at established daycare centres could be an effective alternative. We would develop and test a protocol for management of severe pneumonia on a daycare basis at an established daycare clinic, when hospitalization is not possible due to the lack of hospital beds. Radda MCH-FP Centre at Mirpur, Section 10 has been selected as the site for implementation of the protocol. We already have 12 beds with facilities for oxygen therapy, I/V fluid therapy, suction, bronchodilator, nebulizer, weighing scales, food balance etc. at the Radda MCH-FP Centre. Children attending the out patient department of the Radda MCH-FP Centre, of either gender, aged 1-59 months, with severe or very severe pneumonia and are referred to hospital but not admitted due to lack of beds would be enrolled and treated at the Radda MCH-FP. Parental consent will be required for enrolment in the study. They will remain at the day care centre from 8 A. M. to 5 P.M. and will receive antibiotics and other supportive cares. At 5 P.M. children would be sent home; the same drug would be provided to the parents for continuation of therapy at home until they are brought back to the day care center next morning and would also be instructed to provide other supportive cares. The same treatment will be continued till substantial improvement of the child's condition to allow home management possible. After discharge from the clinic, they would be advised to come for follow up visits every 2 weeks for 3 months. Before the onset of the study protocol, appropriate institutional agreements will be made with I) Dhaka Shishu Hospital (DSH), Dhaka, 2) Institute of Child Health and Shishu Hospital (ICHSH), Mirpur and 3) ICDDR,B Dhaka hospitals for proper management including facilities for hospitalization of the child who become ill at home during the night hours. Child who remains sick at 5 P.M. at Radda MCH-FP Centre will also be admitted at DSH, ICHSH or Dhaka Hospital of ICDDR,B under special circumstances. The collaboration with DSH for admitting study subjects in its hospital has been formalized by identifying Prof. A. K. Azad Chowdury as a co-investigator of the study. The proposal for making arrangements with other hospitals in case beds in DSH are not available has been considered by taking ICHSH as an alternative site for admission of severe cases which could not be managed on a daycare basis and considering Dr. Md. Fazlul Haque (Assistant Prof. & Consultant) of the same hospital as a co-investigator for the study. The admission of study cases requiring hospitalization (which could not be managed on a daycare basis) at DSH/ICHSH/ICDDR,B Dhaka hospitals would be ensured by accompanying project staffs like research assistants, health workers, even in paying beds, if necessary and the cost will be provided from the study. This is actually a collaborative study between ICDDR,B, Radda MCH-FP Centre, DSH, ICHSH and University of Basel, Switzerland with Radda MCH-FP Centre as the primary site for the study.

Response to Attachment 1 a:

1. Children under the age 5 years will be the study subjects as severe and very severe pneumonia is common among them and their mortality rate is very high.
2. No potential risk to the study children.
3. Not applicable as there is no potential risk.
4. All the information obtained from the study children would be kept confidential and stored in a safe place, under lock and key. None other than the staff of this study and regularity authorities such as Ethical Review Committee of ICDDR,B would have an access to those information. The name or identity of the study child would not be disclosed while publishing the results of the study.

Revised on: 19 November 2002

5. Signed informed consent for participating in the study would be obtained from the authorized legal guardian or parents of all study children. Informed consent would be obtained before the enrollment of the child in the study at the Radda MCH-FP Centre in presence of a witness who is not related to the study. Project staff would explain the whole procedure and also any words or information that parents/guardians do not understand before obtaining the consent.
6. Not applicable.
7. All the study children suffering from severe or very pneumonia will be benefited by the standardized management which would include parenteral antibiotics and other supportive cares. After successful completion of the study, established day care clinics with good facilities will be identified for the implementation of the day care management of severe pneumonia thus benefiting the society children.
8. We will only use the hospital records of the study children.

RESEARCH PROTOCOL
Protocol No. 2002-036

FOR OFFICE USE ONLY

RRC Approval: ☐ Yes / ☐ No Date:

ERC Approval: ☐ Yes / ☐ No Date:

AEEC Approval: ☐ Yes / ☐ No Date:

Project Title: Daycare-based management of severe pneumonia in under 5 children when hospitalization is not possible due to the lack of beds

Theme: *(Check all that apply)*

- ☐ Nutrition
- ☐ Emerging and Re-emerging Infectious Diseases
- ☐ Population Dynamics
- ☐ Reproductive Health
- ☐ Vaccine evaluation
- ☐ HIV/AIDS
- ☐ Environmental Health
- ☐ Health Services
- ☒ Child Health
- ☒ Clinical Case Management
- ☐ Social and Behavioural Sciences

Key words: Severe pneumonia, children, day care management

Relevance of the protocol: As management of severe and very severe pneumonia require hospitalization for parentral antibiotics and other supportive cares like suction, oxygen therapy, bronchodilator, nebulizer and the number of hospital beds are inadequate in Bangladesh and other developing countries for admission of all pneumonia cases that require hospitalization, it would be relevant to find out an effective alternative like provision of parental antibiotics and supportive cares during the period of stay at established daycare centers when hospitalization is not possible due to bed constraints, at least until stabilization of their acute conditions since mortality among children with severe pneumonia is highest during the initial phase of illness. Therefore, it would be highly relevant to develop and test a protocol for management of severe pneumonia based on the WHO recommended ARI management in under 5 children on a daycare basis at an established daycare clinic, when hospitalization is not possible due the lack of beds in hospitals.

Programmes

- ☒ Child Health Programme
- ☐ Nutrition Programme
- ☐ Programme on Infectious Diseases & Vaccine Science
- ☐ Health and Family Planning Systems Programme
- ☐ Population Programme
- ☐ Reproduction Health Programme

Principal Investigator: Dr. Hasan Ashraf **Division:** Clinical Sciences Division **Phone:** 8811751-60 Ext. 2313
Address: ICDDR,B:Centre for Health and Population Research **Email:** ashrafh@icddrb.org
GPO Box # 128, Dhaka 1000, Bangladesh

Co-Principal Investigator(s): None

Co-Investigator(s): Dr. N. H. Alam , CSD, ICDDR,B
Drs. S. M. Mohiuddin Kamal, A. I. Begum, Rokhsana Mahmud, Radda MCH-FP Centre, Dhaka
Prof. A. K. Azad Chowdury, Dhaka Shishu Hospital
Dr. Md. Fazlul Haque, Institute of Child Health & Shishu Hospital, Mirpur, Dhaka
Prof. Klaus Gyr, University of Basel, Switzerland

Student Investigator/Intern: None

Collaborating Institute(s): Radda MCH-FP Centre, Dhaka
Dhaka Shishu Hospital, Dhaka
Institute of Child Health & Shishu Hospital, Mirpur, Dhaka
University of Basel, Switzerland

Population: Inclusion of special groups *(Check all that apply)*:

Gender
- x Male
- x Females

Age
- ☒ 0 – 5 years
- ☐ 5 – 9 years
- ☐ 10 – 19 years

- ☐ Pregnant Women
- ☐ Fetuses
- ☐ Prisoners
- ☐ Destitutes
- ☐ Service providers
- ☐ Cognitively Impaired
- ☐ CSW

Revised on: 19 November 2002

☐ 20 – 64 years
☐ 65 +

☐ Others (specify _____)
☐ Animal

Project / study Site *(Check all the apply)*:

☐ Dhaka Hospital
☐ Matlab Hospital
☐ Matlab DSS area
☐ Matlab non-DSS area
☐ Mirzapur
☒ Dhaka Community
☐ Chakaria
☐ Abhoynagar
☐ Mirsarai
☐ Patyia
☐ Other areas in Bangladesh _____
☐ Outside Bangladesh
name of country: _____
☐ Multi centre trial
(Name other countries involved)
_____

Type of Study *(Check all that apply)*:

☐ Case Control study
☐ Community based trial / intervention
☐ Program Project (Umbrella)
☐ Secondary Data Analysis
☒ Clinical Trial (Hospital/Clinic)
☐ Family follow-up study
☐ Cross sectional survey
☐ Longitudinal Study (cohort or follow-up)
☐ Record Review
☐ Prophylactic trial
☐ Surveillance / monitoring
☐ Others

Targeted Population *(Check all that apply)*:

☒ No ethnic selection (Bangladeshi)
☐ Bangalee
☐ Tribal groups
☐ Expatriates
☐ Immigrants
☐ Refugee

Consent Process *(Check all that apply)*:

☒ Written
☐ Oral
☐ None
☒ Bengali language
× English language

Proposed Sample size:

Sub-group _____ ☐
_____ ☐
Total sample size: 310 _____ ☐
_____ ☐
_____ ☐

Determination of Risk: Does the Research Involve *(Check all that apply)*:

☐ Human exposure to radioactive agents?
☐ Fetal tissue or abortus?
☐ Investigational new device?
(specify _____)
☐ Existing data available from Co-investigator
☐ Human exposure to infectious agents?
☐ Investigational new drug
☐ Existing data available via public archives/source
☐ Pathological or diagnostic clinical specimen only
☐ Observation of public behaviour
☐ New treatment regime

Yes/No

☒ ☐ Is the information recorded in such a manner that subjects can be identified from information provided directly or through identifiers linked to the subjects?

☐ ☒ Does the research deal with sensitive aspects of the subject's behaviour; sexual behaviour, alcohol use or illegal conduct such as drug use?

Could the information recorded about the individual if it became known outside of the research:

☐ ☒ a. place the subject at risk of criminal or civil liability?

☐ ☒ b. damage the subject's financial standing, reputation or employability; social rejection, lead to stigma, divorce etc.

Do you consider this research *(Check one)*:

☐ greater than minimal risk
☐ no risk
☒ no more than minimal risk
☐ only part of the diagnostic test

Minimal Risk is "a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as a part of routine physical examination".

Yes/No

☒ ☐ Is the proposal funded?

If yes, sponsor Name: University of Basel, Switzerland

Yes/No

☐ ☐ Is the proposal being submitted for funding ?

If yes, name of funding agency: (1) _____

(2) _____

Do any of the participating investigators and/or their immediate families have an equity relationship (e.g. stockholder) with the sponsor of the project or manufacturer and/or owner of the test product or device to be studied or serve as a consultant to any of the above?

IF YES, submit a written statement of disclosure to the Director.

Dates of Proposed Period of Support	**Cost Required for the Budget Period ($)**			
(Day, Month, Year - DD/MM/YY)	*a. Ist Year*	*2nd Year*	*3rd Year*	*Other years*
Beginning date: 01.01.2003	**26,318**	**29,436**	_____	_____
End date: 31.12.2004	*b. Direct Cost :* **44,491**		*Total Cost :* **55,613**	

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.

Mohammed Abdus Salam
Name of the Division Director

Signature

03 December 2002
Date of Approval

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.

Signature of PI _____

Date: 3-12-2002

Name of Contact Person (if applicable)

_____

Table of Contents

☐ Check here if appendix is included

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

Principal Investigator: Dr. Hasan Ashraf

Project Name: Daycare-based management of severe pneumonia in under- children when hospitalization is not possible due to the lack of beds

Total Budget: US$ 55,613 Beginning Date: 01.02.2003 Ending Date: 31.01.2005

Pneumonia is an infection of the lungs, most commonly caused by viruses or bacteria; however, most serious episodes in children are generally caused by bacteria, and *Streptococcus pneumoniae* and *Haemophilus influenzae* are the two most important among them. Depending on clinical presentation, pneumonia can be classified as very severe, severe, or non-severe, with specific treatment for each of them except for antibiotic therapy, which is indicated irrespective of the severity. In under-five children, the most of the deaths from severe pneumonia occur during the acute phase of treatment (first five days). Severe and very severe pneumonia require hospitalization for additional supportive treatment like suction, oxygen therapy, and administration of bronchodilator. In Bangladesh, the number of hospital beds are inadequate for admission of all pneumonia cases that require hospitalization; however, it is also important to provide institutional care to those children who cannot be hospitalized due to bed constraints, at least until stabilization of their acute conditions since mortality among children with severe pneumonia is highest during the initial phase of illness. Provision of broad spectrum antibiotics, appropriate supportive care during the period of stay at established daycare centres could be an effective alternative. We would develop and test a protocol for management of severe pneumonia, based on the WHO-recommended ARI management in under-5 children, on a daycare basis at an established daycare clinic, when hospitalization is not possible due to the lack of hospital beds. Children attending the out patient department of the Radda MCH-FP Centre, of either gender, aged 1-59 months, with severe or very severe pneumonia according to WHO criteria, and are referred to hospital but not admitted due to lack of beds would be enrolled and treated at the Radda MCH-FP centre on a daycare basis. Parental consent will be required for enrolment of each child in the study. They will remain at the day care centre from 8 A. M. to 5 P.M. under observation, and will receive antibiotics and other supportive cares. At 5:00 p.m. children would be discharged from the day care center; however, they same drug would be provided to the parents for continuation of therapy at home until they are brought back to the day care center the next morning and would also be instructed to provide other supports. The same treatment will be continued till the improvement of the child's condition. After discharge from the clinic, they would be advised to come for follow up visits every 2 weeks for 3 months.

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

Name	Professional Discipline/ Specialty	Role in the Project
1. Dr. Hasan Ashraf	Internal Medicine/Paediatrics	Principal Investigator
2. Dr. N.H. Alam	Internal Medicine/Gastroenterology	Co-Investigator
3. Dr. S.M. Mohiuddin Kamal	Internal Medicine	Co-Investigator
4. Dr. A.I. Begum	Internal Medicine	Co-Investigator
5. Dr. Rokhsana Mahmud	Internal Medicine	Co-Investigator
6. Prof. A.K. Azad Chowdury	Paediatrics	Co-Investigator
7. Dr. Md. Fazlul Haque	Paediatrics	Co-Investigator
8. Prof. Klaus Gyr	Internal Medicine/Gastroenterology	Co-Investigator

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 formulation of the hypothesis.

Under the current constraints in timely hospitalization of children for treatment of severe and very severe pneumonia due to lack of hospital beds, we hypothesize that it would be possible to provide effective treatment and care to under five children with severe and very severe pneumonia at an established daycare clinic in Bangladesh, when efforts for their hospitalization has failed due to the lack of hospital beds.

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 general aim of this protocol is to develop and test a protocol for day-care-based management of severe and very severe pneumonia in under five children, in accordance with a modified WHO-recommended ARI management (5,11,14), at a daycare clinic, when their hospitalization is not possible due to the lack of beds. The specific aim of the protocol is to:

1. assess if it would be possible to efficiently manage children with severe pneumonia on a day care basis at a day care clinic.

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).**

Acute lower respiratory infections (ALRI), particularly pneumonia is the leading cause of childhood morbidity and deaths in the developing countries including Bangladesh (1). Acute respiratory infections (ARI) cause more than 2.7 million child deaths worldwide each year; most of these deaths are due to pneumonia and 99% of them occur in less-developed countries (2-4). Although bronchiolitis, tracheobronchitis and pneumonia, each accounts for about one-third of ALRI cases, pneumonia is responsible for most ALRI deaths. Three studies which reported the diagnosis in children who died of ALRI revealed that a median of 89% (range 71% to 100%) of ALRI deaths were associated with pneumonia (5-7). In Bangladesh, ALRI account for 25% of under-five deaths and 40% of infantile deaths (8). In a study conducted at the Dhaka Hospital of ICDDR,B in 1986-88 among 401 under-five children with ALRI, it has been observed that the most common manifestation was pneumonia, and a respiratory pathogen was identified in 30% cases. The case fatality rates were 14% in bacterial pneumonia and 3% in viral pneumonia (9). The bacterial variety of pneumonia is more prevalent in Bangladesh especially in cases of severe and very severe pneumonia (9). The fatality rate of severe ALRI in children aged 1-4 years is 10-15 times higher in developing than in developed countries (10-11). Highest case-fatality from severe pneumonia among children aged 5 years or less occur during the acute phase of treatment (first five days). It is an infection of the lungs, most commonly caused by viruses or bacteria; however, the most serious episodes in children are generally caused by bacteria in developing countries including Bangladesh. In children, the major causes of pneumonia are *Streptococcus pneumoniae* and *Haemophilus influenzae* (12-13). Specific WHO recommendations for treatment of pneumonia are based on data that *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common causes of bacterial pneumonia in developing countries. Proper management of children presenting in health centres and hospitals with respiratory symptoms is the cornerstone of acute respiratory infections control. It is usually not possible to determine the specific cause by either clinical or chest X-ray features. Depending on clinical presentation pneumonia can be classified as very severe, severe, or non-severe, with specific treatment for each of them (5,11,14). The WHO defines very severe pneumonia as clinical symptoms and signs of pneumonia (cough or difficulty breathing with subcostal recession) with cyanosis or inability to drink (signifying hypoxaemia or severe respiratory distress) (14). Antibiotic therapy is indicated irrespective of the severity of pneumonia. Severe and very severe pneumonia require hospitalization for additional supportive treatment like suction and close monitoring, oxygen therapy, bronchodilator, nebulizer as well as fluid and nutrition management. In Bangladesh, the number of hospital beds are inadequate for admission of all pneumonia cases that require hospitalization; however, it is also important to provide institutional care to those children who cannot be hospitalized due to bed constraints, at least until stabilization of their acute conditions since mortality among children with severe pneumonia is highest during the initial phase of illness. If such children are sent home with antibiotics, it would be important to establish an expensive, home follow up system, without which a significant proportion of them would be expected to have a fatal outcome. Provision of broad spectrum antibiotics, appropriate supportive care during the period of stay at established daycare centres could be an effective alternative. We would develop and test a protocol for management of severe pneumonia based on the WHO recommended ARI management (5,11,14) in under 5 children on a daycare basis at an established daycare clinic, when hospitalization is not possible due the lack of beds in hospitals. We have selected the daycare centre at Mirpur, Section 10, Dhaka, Bangladesh operated by the Radda MCH-FP Centre as the site for implementation of the proposed protocol for management of severe pneumonia. The estimated catchment population of Radda MCH-FP centre is about

1.5 million. Currently, this centre provides primary care for common childhood illnesses including pneumonia on an outpatient basis. The severe pneumonia or very severe pneumonia cases requiring hospitalization are usually referred to DSH for admission, many of whom are refused admission due to lack of beds available at DSH. About 3000 children with a clinical diagnosis of pneumonia visit the day care centre each year, and about 200 of them are diagnosed to be cases of severe or very severe pneumonia requiring hospitalization.

Rationale

Since mortality among under 5 children with severe pneumonia is highest during the acute phase of treatment (initial 1-5 days), failure to provide appropriate institutional care is expected to increase the risk of death among these children if they are asked to continue only antibiotics in home due to inadequacies of hospital beds. Provision of broad spectrum antibiotics, appropriate supportive care at established daycare centres could be an effective alternative for children with severe pneumonia who cannot be hospitalized due to bed constraints. This could potentially be a more cost effective intervention.

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 of individuals during any situations or materials that may be injurious to human health. The methodology section should be sufficiently descriptive to allow the reviewers to make valid and unambiguous assessment of the project. **(DO NOT EXCEED TEN PAGES, USE CONTINUATION SHEETS).**

Study design

It would be highly unethical to conduct a randomized, controlled trial to compare the efficacy of the hospital based treatment with that of the daycare based treatment of children with severe or very severe pneumonia. Thus, children attending the out patient department of the Radda MCH-FP Centre at Mirpur Section 10 will be evaluated for inclusion into the study, and those fulfilling the eligibility criteria will be referred to Dhaka Shishu (Children's) Hospital (DSH) for admission. Those who are not admitted to the DSH due to unavailability of beds would be enrolled in the study after obtaining written informed consent of their parents. An estimated 400 (200/year) children will need referral for hospitalization at DSH for severe or very severe pneumonia, we expect to enroll at least 300 (150/year) children during our 2-year study period at the Radda MCH-FP Centre. We will compare the outcomes such as the duration of illness/hospitalization, development of complications, weight gain, death rate and cost of treatment of children receiving hospital-based care with those receiving the alternative daycare-based care at a daycare clinic over the study period.

Sample size

We estimated the sample size on the mortality of 19% from pneumonia and severe pneumonia (Baqui AH et al., Bull WHO-Ref. 8) and its reduction to 9% with the study intervention. With 90% power and 5% significance, the required sample size has been estimated to be 248 patients. To allow for 20% dropouts due to any reason, a total of 310 children would be required to be enrolled at Radda MCH-FP Centre.

Staff for management of the children at the day care center

Doctors, nurses and health workers would be trained on the management of children with severe pneumonia, and subsequently they would provide care to children enrolled in the study at the Radda MCH-FP Centre The health workers will also be trained to prepare diets and feed children, and educate and motivate mothers to comply with therapies and follow up.

Key Activities

1. Identification of cases of severe or very severe pneumonia among under 5 children attending the out-patient department of Radda MCH-FP Centre
2. Referral of children with severe and very severe pneumonia to DSH
3. Enrollment of children into the study who fulfills the eligibility criteria but refused admission at DSH due to lack of beds
4. Management of severe childhood pneumonia at a daycare clinic
5. Appropriate antibiotic therapy
6. Appropriate supportive care
7. Provision of antibiotic and other drugs, and advice for home management of the patients during the night hours and motivation for follow up visits each morning
8. Subsequent follow up system at home when day care management is over and children do not show up for clinic follow up

Inclusion criteria

- Age: 1 to 59 months
- Gender: Boys and girls
- Suffering from severe or very severe pneumonia according to WHO criteria as defined below (5,11,14):
    - Severe pneumonia-cough or difficult breathing with lower chest chest wall indrawing (with or without fast breathing)
    - Very severe pneumonia-cough or difficult breathing with one or more danger signs (convulsions, drowsiness, inability to drink, stridor in calm child, and severe clinical malnutrition)
    - Non-severe pneumonia-cough or difficult breathing with fat breathing (respiratory rate ≥50 breaths per minute for children aged 2-11 months; ≥40 breaths per minute for children aged 12-59 months); non-severe pneumonia cases will not be included in the study
- Refused admission at DSH due to lack of beds after proper referral

Exclusion criteria

- H/O taking antibiotic drugs for pneumonia during the illness
- Chronic illness like tuberculosis
- Congenital deformities/anomalies
- Severe malnutrition (defined as the weight for height < - 3 z score of NCHS median)
- Trauma/burn
- Bronchiolitis

- Bronchial Asthma
- Lack of parental consent

Attendance in the day care center

Children aged 1-59 months of both gender suffering from severe or very severe pneumonia according to WHO criteria will be admitted on a day care basis at the Radda MCH-FP centre provided they are refused hospitalization. Parental consent will be taken before enrolment into the study. Parents/guardians would be asked to bring their children to the center at 8:00 A.M. each day and to take them home at 5:00 P.M. in the afternoon including weekends and holidays, until resolution of the acute illness and stabilization of their general condition. They will be treated with appropriate antibiotics and supportive cares like suction, oxygen therapy, bronchodilator etc. The children will be nebulized with rapid-acting bronchodilator, if necessary. All children will stay at the day care centre from 8:00 A.M.-5:00 P..M. and receive antibiotics and other supportive cares. The same drug and supportive care will be supplied to the parents at 5:00 P. M. each day for night hours to be taken at home. The same treatment will be continued till substantial improvement of the child's condition to allow home management possible. After discharge from the clinic, they would be advised to come for follow up visits every 2 weeks for 3 months. If any child fails to show up at the follow up visit, a health worker will visit her/his home the next day and motivate her/his parents/guardian to comply with the follow up. The transportation of the children between the Radda MCH-FP Centre and home during the winter months will be done by locally available transport e.g. rickshaws. For maintaining body heat, infants will be covered with warm blankets provided by the study. Mothers will also be trained to hold young infants by "Kangaroo mother care" method during transportation from the centre to the home.

Antibiotic therapy (May be modified depending on changing resistance pattern of common bacterial pathogens)

Clinically diagnosed children with pneumonia will receive parenteral chloramphenicol 75-100 mg/kg per day in 4 equally divided doses. The mothers/attending caretakers will be provided with the night doses to be administered to the children in home. Antibiotic treatment would continue for 7 to 10 days, depending on response to therapy. In the event the condition of the children deteriorate within 24 hours, or if no improvement is noted after completion of 48 hours of therapy, or if there is a suspicion of septicemia, chloramphenicol will be replaced by intramuscular or intravenous ceftriaxone 100 mg/kg to be given as a once daily dose for at least 5 days. If a child fails to attend the day-care centre on any day during the acute phase, a health worker will visit the child at home on the following morning. The reasons for the default will be ascertained, and the child will be escorted to the centre on that day.

Nutritional therapy

Feeding of study children will have two components: at day care centre and at home during the night period.

Diet at the day care centre: As children with severe or very severe pneumonia can become overloaded with fluids easily, they (less than 12 months of age) will receive milk suji (67 kcal and 1.4 g protein /100 ml; appendix 1), 10 ml/kg per feed every 2 hours, at least 4 feeds from morning till 5:00 P.M. before leaving the day care centre. Children aged 12 months to 5 years will receive milk suji, 8 ml/kg per feed every 2 hours at least 4 feeds from morning till 5:00 P.M. before leaving the day care centre. The milk suji will be given by nasogastric tube, if the child is in respiratory distress. This feeding schedule at the day care centre will continue till the resolution of acute illness. Breast-feeding will be continued in all breast-fed children. Measured amount of khichuri/rice curry will be provided to older children, if necessary.

Diet at home during night period: Mothers/caretakers of children will be provided with 3-4 feeds of milk suji in a hot pot with advice to feed the child at specified intervals during the night (between 5:00 P.M.-8:00 A.M.). This feeding schedule during the night hours will also continue every day till the resolution of acute illness. A hot pot will be provided to each mother for taking diet for the night period. The mother/caretaker will be advised to feed the supplied amount of milk suji during night hours and next morning till 8:00 A.M.

The amount left over in the hot pot will be deducted from the supplied amount to obtain the actual amount taken at home on a regular basis. Breast-feeding will also be continued in breast fed children. Similarly, Measured amounts of khichuri/rice curry will be supplied to the mother for older children. The mother/caretaker will be advised on the importance of giving the feeds at night.

Oxygen therapy

Oxygen will be given to children with severe pneumonia with associated hypoxia. The oxygen saturation will be monitored regularly before and after oxygen administration by using pulse oximeter. Oxygen supplies will be made available continuously at all times. Oxygen therapy will be continued until the signs of hypoxia (such as severe lower chest wall in drawing, respiratory rate >70/minute, head nodding, or cyanosis) disappear or the oxygen saturation will be more than 95% without oxygen therapy.

Criteria for oxygen therapy

- Central cyanosis
- The child is unable to drink (due to ALRI)
- Restlessness
- Severe lower chest wall in drawing
- Grunting respiration
- Respiratory rate >70 per minute
- Head nodding

Suction

Any thick secretions in the throat and nostrils will be removed by gentle suction given by an electric sucker machine, and mothers of such children would be educated on how to clear the secretion using finger covered with soft cloth.

Bronchodilator

If wheeze is present, a rapid-acting oral bronchodilator, salbutamol: 1 mg 8 hourly for children below 1 year and 2 mg 8 hourly for children aged 1-5 years will be given. Doses during the stay at home will be supplied to the mother/caretaker at 5:00 P.M. every day.

Bronchodilator by nebulizer

For the purpose of immediate response, a rapid-acting bronchodilator, salbutamol will be administered by nebulizer. The response will be assessed after 15 minutes. If respiratory distress persists, the administration

will be repeated. A decision on the child's condition will be made on the basis of an assessment carried out at least 30 minutes after the last administration of the bronchodilator, since some children will respond then deteriorate quickly. Children who will remain in respiratory distress after a rapid-acting bronchodilator, nebulized salbutamol will be continued every 4 hours, if there is a good response. If necessary, it will be given every 2 hours. Aminophylline will be added only for children with suspected asthma whose bronchospasm is not adequately controlled with nebulized salbutamol every 2 hours. As the severity of the attack will decrease, salbutamol will be given orally instead of nebulizer.
Dose: As all children are under 5 years, we will use 0.5 ml liquid salbutamol, stock solution of which contains 5 mg/ml.

Criteria for nebulization

- Presence of wheeze
- Presence of rhonchi on auscultation
- Severe respiratory distress (respiratory rate >70 per minute)
- Grunting respiration

Management of complication(s)

During the study period, any children developing life-threatening complications such as pneumothorax, pleural effusion, empyema, or those with pulmonary tuberculosis will be referred to the emergency department of DSH for further management under special arrangement. Children, who will develop diarrhoea associated complications (e.g. severe electrolyte(s) imbalance, colitis, ileus etc.) at any time during the study, will be transferred to the Dhaka Hospital of ICDDR,B and managed according to the routine management available at ICDDR,B. Other minor common complications will be managed at the day care centre according to WHO guidelines. Children referred to other hospitals will be followed up regularly by the study staff for keeping record of their final outcomes.

Management of child who become ill at night

Before the onset of the study protocol, appropriate institutional agreements will be made with DSH and ICDDR,B Dhaka hospitals for proper management including facilities for hospitalization of the child who become ill at home during the night hours. Child who remains sick at 5:00 P.M. at Radda MCH-FP Centre will also be admitted at DSH or Dhaka Hospital of ICDDR,B under special circumstances. The requirements of such hospitalization would be considered as a secondary outcome variable of the study and the outcome of such children will be compared with those not requiring hospitalization.

Steps for the recognition of serious signs/symptoms, transportation and admission at DSH/ICDDR,B Dhaka Hospital

The mothers will be educated to watch for the following signs/symptoms and return their child quickly for hospitalisation for the following conditions:

- Breathing becomes difficult
- Breathing becomes fast
- Child is not able to drink
- Child becomes sicker
- Child develops convulsion

- Child becomes drowsy
- Stridor develops in calm child

The transportation of the children from home to the above hospitals will be done by locally available transport e.g. rickshaws.

Provision for health education for mothers on management of pneumonia

The health education for mothers will be provided during their stay at the day care centre, which will cover for the supportive cares and careful observation for the signs/symptoms of severe pneumonia. Regarding feeding the child will include feeding during the illness, increased feeding after illness, clearing the nose with finger covered with soft clothes. Mother will also be asked to offer extra drinks and increase breast milk intake during the course of the illness. As discussed in the previous section (pages 12,13) mothers will be educated to watch for the above signs/symptoms and return their child quickly for hospitalisation.

Strategy for follow up of children who would be refused admission at the Radda MCH-FPCentre

We will arrange follow up of all the children who would be refused admission at the Radda MCH-FP Centre like our enrolled study patients who would be discharged from the Radda Centre after improvement. They will be asked for follow up visits every fortnightly for 3 months like our discharged cases. If any of these child fails to come for follow up visit on his/her date of follow up, a study health worker will visit his/her home on the following morning. The reasons for the default will be ascertained and the child will be escorted to the Radda Centre on that day. It may be mentioned that the addresses of all the children will be recorded in a registrar on the day of refusal of admission with their specific dates for follow up visits.

Replication and future directions

After the successful completion of the study, sustainability of the protocol at the Radda clinic will be evaluated; only Radda staffs and facilities will be used without the project staff and facilities. Then well established day care clinics with good facilities will be identified for the implementation of the day care management of severe pneumonia. Efforts will be made for special arrangements available in typical clinic settings with modification of staff and other logistic facilities. The facilities of the identified clinics will be improved by making arrangements like suction therapy, oxygen therapy, I/V fluid therapy, bronchodilator, nebulizer, pulse oximeter before the initiation of the service. Clinic staffs (doctors, nurses, and health workers) will be trained for conducting such day care management of severe pneumonia.

Outcome variables

Primary — Case fatality rate

Secondary

- Duration of illness
- Failure to treatment on day care basis
- Development of complications
- Requirement of subsequent hospitalisation
- Patient's compliance at day care clinic
- Cost of treatment
- Compliance to home therapy

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).**

We have selected the daycare centre at Mirpur, Section 10, Dhaka, Bangladesh operated by the Radda MCH-FP Centre as the site for implementation of the proposed protocol for management of severe pneumonia in children under five years due to either poor referral practices or compliance by caretaker. Currently, this centre provides primary care for common childhood illnesses including pneumonia on an outpatient basis. The severe pneumonia or very severe pneumonia cases requiring hospitalization are usually referred to DSH for admission, many of whom are refused admission due to lack of beds available at DSH. About 3000 children with a clinical diagnosis of pneumonia visit the day care centre each year, and about 200 of them are diagnosed to be cases of severe or very severe pneumonia requiring hospitalization. The nutrition unit of this centre provides nutrition support to severely malnourished children. Since October 2000, we are conducting the daycare management of severe malnutrition protocol at the Radda MCH-FP Centre with modification of staff and other logistic support from 8:00 A.M. to 5:00 P.M. 7 days a week including holidays. Till date we have successfully managed and followed up 216 severely malnourished children with acute illness at Radda MCH-FP Centre on a day-care basis. The daycare-based severe pneumonia protocol will also be conducted at the Radda MCH-FP Centre with further modification of staff and other logistic facilities. The collaboration with Dhaka Shishu Hospital (DSH) for admitting study subjects in its hospital has been formalized by identifying Prof. A. K. Azad Chowdury as a co-investigator of the study. The proposal for making arrangements with other hospitals in case beds in DSH are not available has been considered by taking Institute of Child Health & Shishu Hospital (ICHSH), Mirpur as an alternative site for admission of severe cases and considering Dr. Md. Fazlul Haque (Assistant Prof. & Consultant) of the same hospital as a co-investigator for the study.

Data Analysis

Describe plans for data analysis. Indicate whether data will be analyzed by the investigators themselves or by other professionals. Specify what statistical software 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).**

SPSS windows program will be used. We will use Student's *t* or Mann-Whitney *U* tests to compare group differences, and categorical variables will be tested by X^2 or Fisher's exact test. We will calculate odds ratios with 95% CIs for selected outcomes. Stepwise logistic regression will also be done if needed. Dropout children will also be included in the analysis up to time of dropout. A supplementary analysis excluding the children withdrawn may also be performed.

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.

Written, informed consent would be required for participation of each patient in the study, which would be conducted according to Good Clinical Practices (GCP), and the Declaration of Helsinki and relevant national guidelines with prior approval by the RRC and ERC. Before enrolment, mothers will be informed about the health status of their child-whether s/he is suffering from severe or very severe pneumonia, the mortality of which varies from 3 to 14% but majority of them improved with specific treatment. As management of severe or very severe pneumonia requires hospitalization which is not always possible due to lack of beds in our country, we have developed a protocol for the management of severe or very severe pneumonia at Radda MCH-FP Centre on a daycare basis. The child will stay at the Radda day care centre from 8:00 A.M. to 5:00 P.M. every day and will receive standard treatment for severe pneumonia like antibiotics and other supportive cares. The same drug and supportive care will be supplied at 5:00 P.M. daily for night hours to be taken at home. The danger signs for children suffering from pneumonia like convulsions, drowsiness, inability to drink, stridor in calm child, and severe clinical malnutrition will be informed to the mothers. They will also be trained how to recognize these danger signs at night at home to take the child to hospitals for admission. Mothers will be informed about the institutional agreements with DSH and ICDDR,B Dhaka hospitals for proper management including facilities for hospitalization of the child who become ill at home during the night hours. Child who remains sick at 5:00 P.M. at Radda MCH-FP Centre will also be admitted at DSH or Dhaka Hospital of ICDDR,B under special circumstances.

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.

This study will not use any animal.

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.

1. World Health Organization. *Life in the 21st Century. A vision for all. Geneva*: WHO, 1998:66.
2. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;349:1269-76.
3. Garenne M, Ronsmans C, Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. World Health Stat Q 1992;45:180-91.
4. Mulholl and EK. Magnitude of the problem of childhood pneumonia. Lancet 1999;354:590-2.
5. World Health Organisation. Acute respiratory infections in children: case management in small hospitals in developing countries. WHO/ARI/ 90.5. Geneva: WHO, 1990.
6. World Health Organisation. Technical basis for the WHO recommendations on the management of pneumonia in children at first-level facilities. WHO/ARI/ 91.20. Geneva: WHO, 1991.
7. World Health Organisation. Manual for the surveillance of antimicrobial resistance of *S. pneumoniae* and *H influenzae*: Epidemiological and microbiological methods. Geneva: WHO 1994.
8. Baqui AH, Black RE, Arifeen SE, Hill K, Mitra SN, al Sabir A. Causes of childhood deaths in Bangladesh: results of a nationwide verbal autopsy study. Bull WHO 1998;76(2):161-71.
9. Rahman M, Huq F, Sack DA, Butler T, Azad AK, Alam AN, Radar N, Islam M. Acute lower respiratory tract infections in hospitalized patients with diarrhoea in Dhaka, Bangladesh. Rev Infect Dis 1990;12 (suppl 8):S 899-906.
10. Oyejide O. Review of epidemiological risk factors affecting the pathogenesis of ARI. In: Report of the conference on pathogenesis of acute respiratory infections in the developing world. Washington, DC: BOSTID Research Programme, 1986:33-5.
11. World Health Organisation. A programme for controlling acute respiratory infections in children. Bull WHO 1984;62:47-58.

12. Bahl R, Mishra S, Sharma D, Singhal A, Kumari S. A bacteriological study in hospitalized children with pneumonia. Ann Trop Paediatr 1995;15:173-7.

13. Shann F. Etiology of severe pneumonia in children in developing countries. Ped Infect Dis J 1986;5:247-52.

14. World Health Organisation. Cough or difficult breathing. In: management of the child with a serious infection or severe malnutrition: guidelines for care at the first-referral level in developing countries. Geneva: WHO, 2000:29-44.

15. World Health Organisation. Management of the young child with an acute respiratory infection. Programme for control of acute respiratory infections. WHO, 1991.

Revised on: 19 November 2002

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 programme.

The finding of the study will be disseminated through presenting the result at national, and/or regional and/or international scientific conference(s), and would also through publication in peer-reviewed medical 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)**

This will be a collaborative study between University of Basel, Switzerland, Radda MCH-FP Centre, Dhaka Shishu Hospital, Institute of Child Health & Shishu Hospital and ICDDR,B.

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.

1 Name : Dr. Hasan Ashraf

2 Present position : Associate Scientist

3 Educational background : M.D.
(last degree and diploma & training relevant to the present research proposal)

List of ongoing research protocols
(start and end dates; and percentage of time)

4.1. As Principal Investigator

Protocol Number	Starting date	End date	Percentage of time
2001-003	01.01.2002	30.06.2003	10%
99-042	01.10.2000	31.03.2003	30%

4.2. As Co-Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

4.3. As Co-Investigator

Protocol Number	Starting date	Ending date	Percentage of time
2002-025			5%
2002-034			5%

5 Publications

Types of publications	Numbers
a) Original scientific papers in peer-review journals	11
b) Peer reviewed articles and book chapters	
c) Papers in conference proceedings	
c) Letters, editorials, annotations, and abstracts in peer-reviewed journals	06
d) Working papers	
b) Monographs	

6 Five recent publications including publications relevant to the present research protocol

1) **Ashraf H**, Ahmed S, Fuchs GJ, Mahalanabis D. Persistent diarrhoea: associated infection and response to a low lactose diet. J Trop Pediatr 2002;48:142-8.

2) **Ashraf H**, Mahalanabis D, Mitra AK, Tzipori S, Fuchs GJ. Hyperimmune bovinecolostrum in the treatment of shigellosis in children: a double-blind randomized, controlled trial. Acta Paediatr 2001;90:1373-8.

3) **Ashraf H**, Hildebrand P, Meier R, Beglinger C, Gyr N. Induction of artificial fat maldigestion by tetrahydrolipstatin assessed by the 13C-hiolein breath test in healthy volunteers. A double-blind controlled pilot study. Digestion 2000;62:159-63.

4) **Ashraf H**, Rahman MM, Fuchs GJ, Mahalanabis D. Folic acid in the treatment of acute watery diarrhoea in children: a double-blind, randomized, controlled trial. Acta Paediatr 1998;87:1113-5.

5) **Ashraf H**, Mitra AK, Mahalanabis D, Dhaka, Bangladesh of the International Working group on persistent diarrhoea. Evaluation of an algorithm for the treatment of persistent diarrhoea; a multicentre study. Bull World Health Organ 1996;74:479-89.

APPENDIX

International Centre for Diarrhoeal Disease Research, Bangladesh
Voluntary Consent Form

Title of the Research Project: Daycare-based management of severe pneumonia in under 5 children when hospitalization is not possible due to the lack of beds

Principal Investigator: Dr. Hasan Ashraf

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.

Information for the Study Participant and Consent: Please ask our study staff to explain any words or information you do not understand. If you agree to take part in the study, we will give you a copy of this consent form.

Introduction

Pneumonia is an infection of the lungs, most commonly caused by viruses or bacteria; however, most serious episodes in children are generally caused by bacteria, and *Streptococcus pneumoniae* and *Haemophilus influenzae* are the two most important among them. Depending on clinical presentation, pneumonia can be classified as very severe, severe, or non-severe, with specific treatment for each of them except for antibiotic therapy, which is indicated irrespective of the severity. Severe and very severe pneumonia require hospitalization for additional supportive treatment like suction, oxygen therapy, bronchodilator, nebulizer etc. In Bangladesh, the number of hospital beds are inadequate for admission of all pneumonia cases that require hospitalization. Provision of broad spectrum antibiotics, appropriate supportive care during the period of stay at established daycare centres could be an effective alternative.

Purpose of the study

As management of severe and very severe pneumonia require hospitalization and the number of hospital beds are inadequate in Bangladesh for admission of all pneumonia cases that require hospitalization, it would be relevant to find out an effective alternative to develop and test a protocol for management of severe pneumonia based on the WHO recommended ARI management in under 5 children on a daycare basis at an established daycare clinic, when hospitalization is not possible due the lack of beds in hospitals.

Study Procedures

Your child is suffering from severe or very severe pneumonia. If you allow us to enroll your child in our study, s/he would stay at the Radda MCH-FP Centre from 8:00 A.M. to 5:00 P.M. every day and receive standard treatment for severe pneumonia like parenteral antibiotics and other supportive cares including suction, oxygen, bronchodilator (oral or

by nebulizer), appropriate fluid and nutrition etc. The same drug and supportive care will be supplied at 5:00 P.M. daily for night hours to be taken at home. The same treatment will be continued till the improvement of the child's condition and discharged. The child will be followed up for a period of 3 months every fortnightly. If your child develops any complication or become sick at night that requires hospitalization, we will arrange that at Dhaka Shishu Hospital (DSH) or Institute of Child Health and Shishu Hospital (ICHSH), Mirpur or ICDDR,B, Dhaka Hospital, even in paying beds, if necessary.

Benefits

Other than the protocolized treatment for severe pneumonia that would be available at the Radda MCH-FP Centre, your child/you would not receive any other benefit from participation of your child in this study. However, we will arrange hospitalization of your child to DSH/ICHSH/ICDDR,B Dhaka Hospital, if management at Radda MCH-FP Centre fails or your child develops complications of pneumonia requiring hospital admission.

Risks and procedures to minimize them

No major risk is involved in this study. We will not draw any blood sample from your child. We will only perform a chest x-ray of your child for proper diagnosis of pneumonia.

Rights

You are the only person to decide for and against participation of your child in the study. You may refuse enrollment of your child in the study, and may withdraw your consent at any time during the study without showing any reason and without any penalty.

Alternatives

If your child do not participate in the study, and also if you withdraw your child from the study after initial participation, s/he would receive the usual routine treatment available at the Radda MCH-FP Centre for her/his current as well as future illnesses.

Confidentiality

All the information obtained from your child would be kept confidential and stored in a safe place, under lock and key, and none other than the staff of this study, and regularity authorities such as Ethical Review Committee of ICDDR,B would have an access to those information. The name or identity of your child would not be disclosed while publishing the results of this study.

Compensation

Your child will be treated free of charge but neither you have to pay us nor we would pay you for participation of your child in this study.

Answering parents'/guardians' questions

You would be able to freely ask questions about illness of your child and about the study now, and would also be able to contact the investigators of this study afterwards at the

address given below. We would be happy to provide the x-ray report of your child when available.

If you agree to our request for participation of your child into the study, please indicate that by signing or putting your left thumb impression at the specified space below.

Parents'/guardians' Consent:

I have read this consent form/the investigators have informed me on the details of the research study. Full and satisfactory answers have also been provided to all of my questions. I have also been told that I would be able to ask questions about my child's illness, the x-ray results and about the study.

Patients name:

Patient's I.D. No:

Parent's/Guardians Name	Parents/Guardian's Signature /LTI	Date
Investigator/Representative's Name	Investigator/Representative's Signature	Date
Witness's Name	Witness's Signature	Date

Contact Address of the Investigators

Name:	Telephone Number
Dr. Hasan Ashraf	8811751-60 Ext. 2313
Dr. N. H. Alam	8811751-60 Ext. 2332
Dr. S. M. Mohiuddin Kamal	9000284/8011303Ext. 214
Dr. Rokhsana Mahmud	9000284/8011303 Ext. 208

আর্ন্তজাতিক উদরাময় গবেষণা কেন্দ্র, বাংলাদেশ

ঐচ্ছিক সম্মতি পত্র

গবেষণার শিরোনামঃ ডে-কেয়ার ক্লিনিকে অনুর্ধ ৫ বছর বয়সের শিশুদের মারাত্মক নিউমোনিয়া রোগের চিকিৎসা, যদি শিশুরা হাসপাতালে বিছানার অভাবে ভর্তি হতে না পারে।

ভুমিকাঃ নিউমোনিয়া হচ্ছে ফুসফুসের একটি সংক্রমন, যা সাধারনতঃ ভাইরাস অথবা ব্যাকটেরিয়া দ্বারা হতে পারে। শিশুদের মারাত্মক নিউমোনিয়া সাধারনতঃ ব্যাকটেরিয়া দ্বারা হয়ে থাকে, যেমনঃ স্ট্রেপটোকক্কাস নিউমোনি এবং হিমোফিলাস ইনফ্লুয়েঞ্জি। ক্লিনিক্যাল উপস্থাপনার ভিত্তিতে নিউমোনিয়া কে খুব মারাত্মক, মারাত্মক এবং মারাত্মক নয় এই তিন ভাগে ভাগ করা যায়। এর প্রত্যেকটির জন্য এন্টিবায়োটিক দ্বারা চিকিৎসা করা হয়ে থাকে। খুব মারাত্মক এবং মারাত্মক নিউমোনিয়া রোগীকে হাসপাতালে ভর্তি রেখে চিকিৎসা করা হয়। এই সমস্ত রোগীকে চিকিৎসার জন্য সাকশান, অক্সিজেন, ব্রঙ্কোডাইলেটার, নেবুলাইজার ইত্যাদির প্রয়োজন হয়। বাংলাদেশের মত উন্নয়নশীল দেশের ক্ষেত্রে মারাত্মক নিউমোনিয়ায় আক্রান্ত রোগীর ভর্তির জন্য প্রয়োজনীয় শয্যা সংখ্যার যথেষ্ট অভাব রয়েছে। হাসপাতালের বিকল্প হিসাবে এই সমস্ত মারাত্মক নিউমোনিয়া রোগীকে ডে-কেয়ার ক্লিনিকে রেখে উপযুক্ত চিকিৎসা করা যেতে পারে।

গবেষণার উদ্দেশ্যঃ

খুব মারাত্মক এবং মারাত্মক নিউমোনিয়ার ক্ষেত্রে হাসপাতালে ভর্তির প্রয়োজন হয়। কিন্তু বাংলাদেশে এই সমস্ত রোগীকে হাসপাতালে রেখে চিকিৎসার জন্য যত শয্যার প্রয়োজন হয় তার যথেষ্ট অভাব রয়েছে। সে ক্ষেত্রে হাসপাতালের বিকল্প হিসাবে "প্রতিষ্ঠিত ডে-কেয়ার ক্লিনিকে" রেখে WHO এর নির্ধারিত ARI এর ব্যবস্থাপনা অনুযায়ী পাঁচ বছরের কম বয়সী শিশুদের চিকিৎসা দেয়ার ব্যবস্থা করাই এই গবেষণার উদ্দেশ্য।

গবেষণার পদ্ধতিসমূহঃ

আপনার শিশু মারাত্মক বা খুব মারাত্মক নিউমোনিয়া রোগে ভুগছে। আপনি যদি এই গবেষণায় আপনার শিশুকে অন্তর্ভুক্ত করতে রাজী থাকেন তবে আপনার শিশুকে প্রতিদিন সকাল ৮ টা হতে বিকাল ৫ টা পর্যন্ত রাড্ডা ডে-কেয়ার ক্লিনিকে রেখে চিকিৎসা করা হবে। এই সময়ে শিশু উপযুক্ত এন্টিবায়োটিক ও অন্যান্য Supportive চিকিৎসা পাবে যেমন, সাকশান, অক্সিজেন, ব্রঙ্কোডাইলেটর, নেবুলাইজার ইত্যাদি। একই চিকিৎসা ব্যবস্থা রাতের জন্য আপনাদেরকে প্রদান করা হবে। আপনার শিশু সম্পূর্ণ সুস্থ্য হওয়া পর্যন্ত উপরোক্ত চিকিৎসা চলবে। সুস্থ্য হওয়ার পর ছুটি দেওয়া হবে। ছুটির পর প্রতি ১৫ দিন অন্তর আপনার শিশুকে রাড্ডা ক্লিনিকে Follow Up এর জন্য আসতে হবে। এইভাবে ৩ মাস পর্যন্ত Follow Up করা হবে। যদি আপনার শিশুর কোন জটিলতা দেখা দেয় অথবা অথবা বিকাল ৫ টার পর হতে সকাল ৮ টার মধ্যে যে কোন সময়ে রোগী খুব বেশী অসুস্থ্য হয়ে পড়ে তবে আপনার শিশুকে ঢাকা শিশু হাসপাতালে

অথবা মিরপুর শিশু হাসপাতাল বা কলেরা হাসপাতালে ভর্তি করে চিকিৎসা করা হবে। এমনকি প্রয়োজনবোধে আপনার শিশুকে পেইং বেডে রেখে চিকিৎসা করা হবে।

সুবিধাদিঃ

রাড্ডা ডে-কেয়ার ক্লিনিকে মারাত্মক নিউমোনিয়া রোগীর উপযুক্ত চিকিৎসা ব্যাতীত অন্য কোন সুবিধা দেয়া হবে না। তবে, যদি আপনার শিশুর কোন প্রকার নিউমোনিয়া জনিত জটিলতা দেখা দেয় অথবা ডে-কেয়ার ক্লিনিকের চিকিৎসা ব্যবস্থায় শিশু ভাল না হয়, তবে ঢাকা শিশু হাসপাতাল বা মীরপুর শিশু হাসপাতাল অথবা কলেরা হাসপাতালে ভর্তির ব্যবস্থা করা হবে।

ঝুঁকি ও ঝুঁকি কমানোর পদ্ধতিঃ

গবেষণার অংশ গ্রহনের বড় কোন ঝুঁকি নেই। আমরা আপনার শিশুদের কাছ থেকে কোন রক্ত নেব না। শুধু মাত্র সঠিক নিউমোনিয়া নির্ধারনের জন্য শিশুর বুকের X-ray করা হবে।

গবেষণার অংশগ্রহনকারীর অধিকারঃ

এই গবেষণায় আপনার শিশুর অংশগ্রহন সম্পূর্ণ স্বেচ্ছামূলক। আপনি না চাইলে আপনার শিশুকে এ গবেষণায় অর্ন্তভূক্ত করা হবে না। অংশগ্রহনের পরেও, যে কোন সময়ে আপনি আপনার সম্মতি প্রত্যাহার করতে পারবেন। গবেষণায় অংশগ্রহন না করলে অথবা যে কোন সময়ে আপনি আপনার সম্মতি প্রত্যাহার করলেও শিশুকে এখন ও পরবর্তীতে রাড্ডা ডে-কেয়ার ক্লিনিকে প্রচলিত সুচিকিৎসা দেয়া হবে।

তথ্যের গোপনীয়তা রক্ষাঃ

আপনার রোগীর থেকে পাওয়া তথ্য ও X-ray এর ফলাফল তালাবদ্ধ আলমারীতে গোপন রাখা হবে। এসব তথ্য এই গবেষণায় জড়িত গবেষক ও কর্মী এবং নিয়ন্ত্রনকারী কর্তৃপক্ষ যেমন আই. সি. ডি. ডি. আর., বি.'র "নীতি পর্যালোচনা কমিটি" ছাড়া অন্য কেউ জানতে পারবেন না। গবেষণার ফলাফল প্রকাশের সময় কোথাও আপনার শিশুর নাম অথবা পরিচয়ের উল্লেখ থাকবে না।

ক্ষতিপূরণঃ

বিনামূল্যে আপনার শিশুর চিকিৎসা করা হবে। কিন্তু, চিকিৎসা বাবদ আপনাকে কোন অর্থ খরচ করতে হবে না এবং এই গবেষণায় অংশগ্রহনের জন্য আপনাকেও কোন রকম অর্থ দেয়া হবে না।

গবেষণায় অংশগ্রহনকারীর প্রশ্নের উত্তর প্রদানঃ

আপনার শিশুর অসুখ অথবা এই গবেষণা সমন্ধে কোন প্রশ্ন থাকলে আপনি তা এখন কিংবা পরবর্তীতে করতে পারবেন। আপনি চাইলে পরবর্তীতেও আপনার প্রশ্নের উত্তরের জন্য এই গবেষনার গবেষকদের সাথে নীচের ঠিকানায় যোগাযোগ করতে পারবেন আমাদের জানা সাপেক্ষে, আপনি চাইলে আপনার শিশুর X-ray রিপোর্ট আপনাকে জানানো হবে।

আপনি আমাদের গবেষণায় আপনার শিশুর অংশগ্রহনে সম্মত থাকলে অনুগ্রহ করে নীচের নির্দিষ্ট স্থানে আপনার স্বাক্ষর / বাম বৃদ্ধাঙ্গুলির টিপসই দিন।

মাতা পিতার / অভিভাবকের সম্মতিঃ

সম্মতিপত্র আমি পড়েছি। আমাকে গবেষণার কর্মী এই গবেষণার ব্যাপারে বিস্তারিত জানিয়েছেন। আমার সকল প্রশ্নের সম্পূর্ণ এবং সন্তোষজনক উত্তর দেওয়া হয়েছে। আমাকে এও জানানো হয়েছে যে, পরবর্তীতে আমি আমার শিশুর অসুখ ও তার চিকিৎসার **X-ray** রিপোর্ট এবং গবেষণার ব্যাপারে প্রশ্ন করতে পারবো।

রোগীর নামঃ

রোগীর ক্রমিক নম্বরঃ

_____	_____	_____
অভিভাবকের নাম	অভিভাবকের স্বাক্ষর/টিপসহি	তারিখ
_____	_____	_____
গবেষকের/প্রতিনিধির নাম	গবেষকের/প্রতিনিধির স্বাক্ষর	তারিখ
_____	_____	_____
স্বাক্ষীর নাম	স্বাক্ষীর স্বাক্ষর	তারিখ

গবেষকের সাথে যোগাযোগের ঠিকানা

গবেষকের নাম	**টেলিফোন নম্বর**
ডাঃ হাসান আশরাফ	৮৮১১৭৫১ - ৬০ / ২৩১৩
ডাঃ নুর হক আলম	৮৮১১৭৫১ - ৬০ / ২৩৩২
ডাঃ মহিউদ্দিন কামাল	৯০০০২৮৪ / ৮০১১৩০৩ / ২১৪
ডাঃ রুখসানা মাহমুদ	৯০০০২৮৪ / ৮০১১৩০৩ / ২০৮

Detailed Budget for New Proposal

Project Title: Daycare-based management of severe pneumonia in under 5 children when hospitalization is not possible due to the lack of beds

Name of PI: Dr. Hasan Ashraf

Protocol Number: Name of Division: Clinical Sciences Division

Funding Source: University of Basel, Switzerland Amount Funded (direct): US$44,491 Total:US$ 55,613 Overhead (25%)

Starting Date: 01.01.2003 Closing Date: 31.12.2004

Strategic Plan Priority Code(s):

ICDDR,B Part

Personnel	Effort %	Salary	1st Year	2nd Year	Total
Dr. Hasan Ashraf, PI	10%	1245	1,494	1,569	3,063
Dr. N.H. Alam, Co-Investigator	5%	1415	849	891	1,740
Sr. Research Assistant	100%	225	2,700	2,835	5,535
Field Assistant	100%	142	1,704	1,789	3,493
Sub Total			**6,747**	**7,084**	**13,831**
International travel: To disseminate study findings at Int. Scient. Conf.				3,000	3,000
Sub Total				**3,000**	**3,000**
Supplies and Materials (Description of items)					
Medicines			200	300	500
Office Supplies			100	100	200
Non-stock supplies			100	100	200
Pulse oximeter			710	-	710
Cell phone			917	413	1,330
Sub Totals			**2,027**	**913**	**2,940**
Other Contractual Services					
Email, fax, DHL & other utilities			100	100	200
Printing & Publication			200	200	400
Sub Total			**300**	**300**	**600**
Interdepartmental Services					
Patients food			200	300	500
Sub Total			**200**	**300**	**500**
Total Direct Cost (ICDDR,B)			**9,274**	**11,597**	**20,871**
Subcontract to Radda			**11,780**	**11,839**	**23,619**
Total Direct Cost (ICDDR,B)			**9,274**	**11,597**	**20,871**
Total Direct Cost			**21,054**	**23,436**	**44,490**
Indirect cost (25% Overhead)			**5,264**	**5,859**	**11,123**
Total Project Cost			**26,318**	**29,295**	**55,613**

4/12/02

Md. Bozlur Rahman
Manager, Budget & Costing
ICDDR,B: Centre
Health & Population Research
Mohakhali, Dhaka-1212
Bangladesh

Annex - A

Radda Part

Personnel

Medical Officer, Co-Investigator	100%	260	3,120	3,276	6,396
Study Nurse, Co-ordinator	100%	225	2,700	2,835	5,535
Research Assistant	100%	140	1,680	1,764	3,444
Health Worker - 2	100%	2 x 70	1,680	1,764	3,444
Sub Total			**9,180**	**9,639**	**18,819**
Supplies and Materials (Description of items)					
Medicines			800	700	1,500
Office Supplies			100	100	200
Non-stock supplies			200	200	400
Sub Total			**1,100**	**1,000**	**2,100**
Other Contractual Services					
Repair and Maintenance			100	100	200
Sub Total			**100**	**100**	**200**
Interdepartmental Services					
Patients food			800	700	1,500
Laboratory Test			100	100	200
X-ray			200	100	300
Transport			300	200	500
Sub Total			**1,400**	**1,100**	**2,500**
Total Direct Cost (RADDA)			**11,780**	**11,839**	**23,619**

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.

Budget Justifications

1. Salaries of personnel are requested according to the percentage of work of each person involved in the study.
2. Laboratory costs are estimated as per ICDDR,B and Radda MCH-FP Centre laboratory charge for each test.
3. Capital expenditure includes cost of items considered to be essential to support the study such as computer, printer and accessories, file cabinet etc.
4. Local travel includes the charge for sending the patients to their home.
5. International travel is requested for dissemination of study findings and other study related matters.

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)

1. Protocol Number: 2001-003; Source: University of Basel, Switzerland; Amount: US$ 19,500; Duration: 1 year 6 months.
2. Protocol Number: 99-042; Source: NCOE (World Bank), followed by GOB Gates Match Fund; Amount: US$ 42,000; Duration: 2 years 6 months.

Check List

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

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

Response to the reviewer's comments

Reviewer No. 1

1. **Comment**: The death from pneumonia is very high in young infants that is 1-4 months of age. This being so, it is not clear why the investigators do not include the age group.

   Response: Following reviewer's comment, we are now planning to enroll children 1-59 months of age (instead of earlier suggested 4-59 months), and this had been described under the inclusion criteria (page 9).

2. **Comment**: Under specific aims, it appears that too many aims have been included, in particular they need to clarify how they are going to evaluate the reduction in mortality rate.

   Response: We have reduced the specific aims to only two (instead of five), and comparison of mortality has been dropped as a specific aim (page 6).

3. Comment: *Transportation* – Transportation between the centre and home during winter months need to be described in details e.g., problem of maintaining body heat particularly in young infants should be addressed.

   Response: We would provide blankets to wrap the baby and keep them warm while taking them to an from the Clinic using common transportation system e.g. Rickshaws. Mothers will also be trained on provision of "Kangaroo Care" to the infants during transportation. Description of transportation procedure has been provided on page 10 of the protocol.

4. **Comment**: Exclusion criteria- Please define the severe malnutrition. It is not clear why bronchiolitis would be excluded.

   Response: Severe malnutrition is defined as the weight for height <-3 z score of NCHS median (page 9). Infants and children with bronchiolitis would be excluded because their inclusion would create problems in defining severe and very severe pneumonia and potentially misclassify them.

5. **Comment**: *Diet at home* – I have some apprehension in providing mothers with prepared food in a hot pot. Could this get contaminated at home due to inappropriate handling?

   Response: We do not envision any problem in providing the mothers with prepared food in a hot pot because we are practicing this for the last year and half for our another ongoing study and did not encounter any problem. We have enrolled 216 severely malnourished children in that study and provided them with prepared food in a hot pot, which did not get contaminated after proper orientation of the mothers on handling the supplied food at home.

6. **Comment**: The PI should indicate what the mother should do if a child becomes ill at home in the night.

   Response: Appropriate institutional arrangements will be made with DSH and ICDDR,B Dhaka hospitals for proper management of children who becomes ill at home in the night including

facilities for hospital admission. Parents would be informed on this arrangement. Management of child who become ill at night has also been described in the protocol (page 12).

7. **Comment**: Outcome variables – The PI should provide sample size calculation for the primary outcome.

   Response: The basis for the sample size calculation has been provided in the protocol (page 8).

Reviewer No. 2

1. **Comment**: The objective of this study and the design need to be clear. Is the target only those children (parents) who refuse admission or those for which hospitalization is not possible? This differentiation is critical to understanding the design of the study. If parents refuse then a domiciliary therapy may be feasible with a safety net. Why not attempt this approach with moderate pneumonia cases first and then try this critically ill subgroup? If possible, why not use a phased approach like one used by Bang et al for ambulatory therapy of neonatal sepsis and use appropriate injectable antibiotics.

   Response: We have tried our best to clarify the objective of our study as well as its design. Our target children are those who require hospitalization for their severe and very severe pneumonia yet are refused admission at DSH due to lack of beds (i.e. receiving a seal with written statement "no free beds available, refused admission"). Refusal of admission by parents is not our enrollment criterion. We are interested to examine the effectiveness of an alternate treatment strategy for children with severe and very severe pneumonia who should have received hospitalized care but fail to receive so. We do not intend to examine alternative treatment options for pneumonia of varied severity, and thus a phased approach to initially enroll cases of moderate pneumonia cannot be taken.

2. **Comment**: What is the likelihood of failure of admission to other centers (in the public sector) if admission to Dhaka Shishu hospital is not possible? Will families agree to go home and return on a daily basis to the day care centre? We need clear feasibility data and some pilot information here. The specter of families parking in the open near the hospital waiting for the Radda MCH centre to open next morning is both real and alarming.

   Response: The likelihood of failure of admission to other centers (in the public sector) when admission to Dhaka Shishu hospital would be high. Among public hospitals, the best hope would be to get admitted to the Dhaka Medical College; however, admission to this hospital is much more competitive than admission at DSH and private hospitals. Most of our study patients will come from poor socioeconomic status (SES); 96% children belong to poor SES (i.e. monthly family income of <US$ 40) in our ongoing severe PEM study at Radda MCH-FP centre and therefore would not be able to pay expenses for the private sector either. Yes, families will agree to go home and return on a daily basis to the day care centre. We have taken a similar approach of providing "day care based management" to acutely ill severely malnourished children at the Radda MCH-FP Centre for our ongoing study. We have enrolled 216 severely malnourished children within the last year and a half, and 83% of these children were successfully discharged upon fulfillment of the discharge criteria (improvement of acute illness and nutritional status) (Ref 1). They were also successfully followed up for a period of 3 months with good compliance. We are not very sure about the reviewer's concern "The specter of families parking in the open near the hospital waiting for the Radda MCH centre to open next morning is both real and alarming"! For children already enrolled in the study and sent home for night time management (because the daycare clinic closes at 5:00 p.m.), the parents would know the time the clinic opens and they would not be expected to

come too early and wait in front of the clinic. For enrolled children who becomes critically ill during the night hours, a system would be in place for their admission to DSH or Dhaka Hospital of ICDDR,B (page 12). On the other hand, it would be highly unlikely, in the absence of previous experience of the parents on this new strategy of treatment of severe and very severe pneumonia on a day care basis, that the parents with such children would crowd the clinic early in the morning for admission of their children in the study.

3. **Comment**: What are the ethical issues involved in this study on a very vulnerable group and how they be addressed? The protocol is largely silent on this.

   Response: This study addresses a potential ethical issue in that the study would enroll and provide effective treatment to infants and children refused admission to a hospital. In fact, instead of raising ethical concern, this study aims, in a way, in resolving such issue.

4. **Comment**: We need further support for using oral chloramphenicol in cases of severe pneumonia (as this is not a WHO recommendation for this category, although I appreciate that IMCI guidelines have combined severe and very severe disease). Why not treat these children with once daily IM ceftriaxone in domiciliary setting? Have the relative costs for both strategies been worked out.

   Response: WHO as well as IMCI recommends the use of oral chloramphenicol in the management of severe pneumonia, and they recommend the use of injectable ceftriaxone only if no improvement is noted after 48 hours of chloramphenicol therapy or if there is a suspicion of septicaemia (page 10). WHO/IMCI does not recommend treatment of children with once daily IM ceftriaxone in domiciliary setting, and they both recommend hospitalization of all cases of severe and very severe pneumonia.

5. **Comment**: What culture findings and criteria will be used for diagnosis? How will bronchiolitis and asthma cases be differentiated? What about secondary bacterial infections in the latter cases?

   Response: Septicaemia will be diagnosed clinically, and blood for culture will be sent at the ICDDR,B laboratory before starting therapy for sepsis. The clinical signs and symptoms for sepsis include poor peripheral perfusion with absent radial pulse or rapid and incountable radial pulse, blotchy appearance of the skin, hypotension or unrecordable blood pressure, lethargy, peripheral cyanosis, and associated hypoglycaemia. Similarly, bronchiolitis and asthma cases will be differentiated clinically as well as radiologically.

6. **Comment**: What would be the criteria for nebulizer and oxygen therapy and what will be done at night when the latter are not possible, but necessary? Will such cases not be referred else where or kept in the Dhaka Shishu emergency room.

   Response: Criteria for oxygen and nebulizer therapies have been described in the protocol (page 11). Parents would be instructed to recognize children requiring such therapies and to take them to the DSH or Dhaka Hospital of ICDDR,B in the event they develop such problem during the night hours. Necessary arrangements will be made for admission at night at DSH/ICDDR,B Dhaka hospital (page 12).

7. **Comment**: The nutrition intervention seems secondary to the main study objectives. Currently the IMCI guidelines principally refer to vitamin A supplementation. What micronutrients are proposed in the current protocol?

Response: The nutrition intervention is secondary to the main study objectives; however, they are the integral part of the management of severe and very severe pneumonia. Supplementation of vitamin A would be done following current IMCI guidelines. We are not proposing supplementation of micronutrients; zinc supplementation can be done in one subgroup of patients as it shows positive impact in childhood pneumonia cases in a recently conducted study at ICDDR,B (Brookes A et al.-personal communication).

References

1. Ashraf H, Mahmud R, et al. Daycare-based management of acutely ill severely malnourished children when hospitalization is not possible due to lack of beds. Gut 2002:A555.

2. Cough or difficult breathing. In: Management of the child with a serious infection or severe malnutrition Guidelines for care at the first-referral level in developing countries. WHO 2000/FCH/CAH/00.1:29-44.

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To: Chairman
Research Review Committee (RRC)

From: Dr. Hasan Ashraf
Principal Investigator of protocol # 2002-036
Clinical Sciences Division

Date: 28 January 2003

Sub: Approval of modified version of Research protocol # 2002-036

Thank you very much for considering the modified version of my research protocol #2002-036 entitled "Daycare-based management of severe pneumonia in under 5 children when hospitalization is not possible due to the lack of beds" in the RRC meeting held on 20th January 2003.

I have replied to the comments in chronological order that is attached herewith. I am forwarding herewith the second revised version of the protocol for your approval.

Thank you.

Enc: a/a

Response to modified version of research protocol # 2002-036

a) The protocol should include strategy for follow up of the children who would be refused admission at the Radda MCH-FP Centre.

Response: The strategy for follow up of the children who would be refused admission at the Radda MCH-FP Centre has been described in the protocol (page 13).

b) Specific Aim # 2 should be dropped. Alternately, the design be revised to allow for this.

Response: Specific Aim # 2 has been dropped from the protocol as suggested (page 6).

c) Formal collaboration with Dhaka Shishu Hospital and Institute of Child Health for admission of severe cases needed to be included in the `Facilities Available' section of the protocol.

Response: Formal collaboration with Dhaka Shishu Hospital and Institute of Child Health for admission of severe cases has been included in the `Facilities Available' section of the protocol (page 14).

d) Investigators' response relating to replication and future directions need to be articulated/built in the protocol as well.

Response: Investigators' response relating to replication and future directions has been articulated in the protocol (page 13).

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Memorandum

To: Chairman, Research Review Committee

From: Dr H. Ashraf, PI, Protocol #2002—036

Date: January 8, 2003

Sub: Modified version of the protocol

Thank you very much indeed for forwarding to me the valuable comments of the RRC members on my protocol entitled "Daycare-based management of severe pneumonia in under 5 children when hospitalization is not possible due to the lack of beds" vide your memo of 18 December 2002.

I have replied to the comments in chronological order that is attached herewith. I am forwarding herewith the revised version of the protocol for consideration by the Committee.

Thank you.

Enc: a/a

RRC Response (Protocol # 2002-036)

a) In the background section, the investigators mentioned a higher case fatality in bacterial pneumonia than in viral pneumonia, but had not mentioned which variety is more prevalent in Bangladesh.

Response: The bacterial variety of pneumonia is more prevalent in Bangladesh especially in cases of severe and very severe pneumonia (9). This information has been inserted in the background section (page 7).

b) The catchment population of Radda MCH-FP clinic should be described in the background section of the protocol.

Response: The estimated catchment population of Radda MCH-FP clinic is about 1.5 million has been described under the background section of the protocol (pages 7 & 8).

c) Service statistics on ALRI cases in Radda MCH-FP clinic need to be added in the background section of the protocol.

Response: The service statistics on ALRI cases in Radda MCH-FP clinic has been added in the background section of the protocol (page 8).

d) The investigators could show an estimate on proportion of targeted children expected to be refused for admission in hospitals.

Response: According to the experience of Radda MCH-FP clinic physicians, about 60-70% of targeted children expected to be refused for admission in hospitals.

e) It is assumed that mothers/caregivers will comply with the treatment to be provided for the night and will give support care. However, the issue is whether or not they will be able to assess possible emergencies/complications encountered at night. The protocol did not discuss adequately the steps (recognition of serious signs/symptoms, transportation and admission) that should be followed by the caregiver at home in such a situation. More explanation is needed on what will happen with patients who are not well enough to go home at the time the day care centre closes when beds are not available at a hospital.

Response: Adequate health education will be given by the study nurse co-ordinator and research assistant to the mothers/caregivers during their stay at the day care centre between 8:00 a.m.-5:00 p.m. everyday. It is expected that after the health education, the mothers/caregivers will be able to recognize the serious sign/symptoms and take necessary measures for hospitalization under special

circumstances as described in the protocol (page 12). The patients who are not well enough to go home at the time the day care centre closes will be admitted at DSH/ICDDR,B, Dhaka hospital under special arrangements as discussed in the protocol (page 12). They will be taken to the above hospitals by study staffs like research assistants, health workers for ensuring admission, even in paying beds, if necessary (cost will be provided from the study).

f) Operational definitions for severe, very severe, and less severe pneumonia should be given under inclusion criteria.

Response: Operational definitions for severe, very severe, and less severe pneumonia are given under inclusion criteria (page 9).

g) Ethical assurance section of the protocol is very brief. All relevant information need to be given to the mothers about health status of the child, possible outcomes, danger signs, institutional arrangement and availability of the facilities and mode of emergency services need to be elaborated under this section.

Response: Ethical assurance section of the protocol has been elaborated taking care of all the above points as suggested by the reviewer (page 15).

h) Special arrangements at the Day Care Centre (as proposed in the protocol) will not be available in typical settings. The investigators should focus on activities that would be replicable more broadly.

Response: Special arrangements that will be available at the Day Care Centre (as proposed in the protocol) will not be available in typical settings. But, efforts can be made to make the special arrangements available in typical settings with modification of staff and other logistic facilities. Everything will depend on our study results and then the facilities can be modified accordingly.

i) The protocol should provide future direction if the protocol works.

Response: Future direction- After the completion of the study, sustainability of the protocol at the Radda clinic will be evaluated; only Radda staff and facilities will be used without the project staff and facilities. Then well established day care clinics with good facilities will be identified for the implementation of the day care management of severe pneumonia. The facilities will be improved by making arrangements like suction therapy, oxygen therapy, I/V fluid therapy, bronchodilator, nebulizer, pulse oximeter before initiation of the service. Clinic staffs (doctors, nurses, and other health workers) will be trained for conducting such day care management of severe pneumonia.

j) Provision for health education for mothers on management of pneumonia be included in the protocol.

Response: Provision for health education for mothers on management of pneumonia has been included in the protocol (page13).

k) Sample size should be corrected (it should be 310).

Response: Sample size has been corrected as 310 (page 8).

l) Proposed collaboration with the Dhaka Shishu Hospital for admitting the study subjects in its hospital should be formalized. The PI may consider making arrangements with other hospitals in case beds in Dhaka Shishu Hospital are not available for the severe cases. The PI may consider accepting one co-investigator from the Dhaka Shishu Hospital.

Response: The proposed collaboration with the Dhaka Shishu Hospital for admitting the study subjects in its hospital has been formalized by identifying the consultant, Prof. A. K. Azad chowdury as co-investigator. The proposal for making arrangements with other hospitals in case beds in Dhaka Shishu Hospital are not available has been considered by taking Institute of Child Health & Shishu Hospital, Mirpur as an alternative site for admission of severe cases and taking Dr. Md. Fazlul Haque (Assistant Professor & Consultant) of the same hospital as a co-investigator for the study.

m) Institutional affiliation of the external investigators should be provided.

Response: Institutional affiliation of the external investigators has been provided (page 1).

Memorandum

To: Chairman
Ethical Review Committee (ERC)

From: Dr. Hasan Ashraf
Principal Investigator of protocol # 2002-036
Clinical Sciences Division

Date: 16 February 2003

Sub: Approval of research protocol # 2002-036

Thank you very much for considering my research protocol #2002-036 entitled "Daycare-based management of severe pneumonia in under 5 children when hospitalization is not possible due to the lack of beds" in the ERC meeting held on 5th February 2003.

I have replied to the comments in chronological order that is attached herewith. I am forwarding herewith the modified version of the protocol for your approval.

Thank you.

Enc: a/a

ERC Response (Protocol # 2002-036)

a) On the ERC Face Sheet, item # 1(a), 4(c), and 4(h) should be marked 'YES' instead of 'no'.

Response: On the ERC Face Sheet, item # 1(a), and 4(c) have been marked 'YES' instead of 'no'. Item # 4(h) has already been marked 'YES' in the original version to ERC.

b) It was not clear to the Committee why there is only one 'Specific Aim' although in response to the query of the reviewers, the PI stated (p 29) that specific aims would be reduced to two.

Response: The 'Specific Aims' of the protocol has been changed to two as before (p 6) as suggested by the ERC.