icddr,b
KNOWLEDGE FOR GLOBAL LIFESAVING SOLUTIONS

RRC APPLICATION FORM

RESEARCH PROTOCOL NUMBER: PR-10088

FOR OFFICE USE ONLY

RRC Approval:	☒ Yes /	☐ No	Date:03/02/2011
ERC Approval:	☒ Yes /	☐ No	Date:02/03/2011
AEEC Approval:	☐ Yes /	☐ No	Date:
External IRB Approval:	☒ Yes /	☐ No	Date: 23/08/2011

Name of IRB: Human Research Ethics

Protocol Title: Use of bubble CPAP compared to nasal prong oxygen or humidified high flow in children under five with severe pneumonia and hypoxaemia: a randomized trial

Short title (in 50 characters including space): Bubble CPAP compared to nasal prong oxygen or humidified high flow

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
- ☐ Gender
- ☐ Human Rights
- ☐ Others (please specify_____)

Key words: Buble CPAP, humidified high flow, hypoxaemia, nasal prong, severe pneumonia,

Relevance of the Protocol:

Maintaining Continuous Positive Airway Pressure (CPAP) is a common form of support to patients with respiratory distress admitted to Intensive Care Units (ICU) of industrialized countries. Nasal CPAP (NCPAP) is effective in reducing hypoxemia and contributes to reducing the number of children requiring endo-tracheal intubation and mechanical ventilation. CPAP is most frequently delivered to neonates using conventional mechanical ventilators, which involves much higher costs. There are other ways of delivering CPAP. Bubble-CPAP is a simple, non-invasive delivery system with potential to reduce hypoxemia in neonates with acute respiratory failure. Equipment of bubble CPAP is now available at a fraction of the cost of mechanical ventilators. Bubble-CPAP has several advantages over mechanical ventilation such as lower cost, easier application by nursing staff and lower risk of complications. It therefore has potential as an inexpensive and affordable method of delivering CPAP in developing countries. Moreover, all the necessary equipment could be made locally.

Humidified high flow air / O_2 supplementation has been suggested in case series to be useful in reducing the need for mechanical ventilation in infants with bronchiolitis. However, there have been no randomized trials to compare it with bubble CPAP or with standard O_2 supplementation by nasal prongs. It is simple to apply, but requires careful monitoring and delivers uncertain levels of CPAP.

Hypoxaemia is documented in nearly half of the patients admitted to the ICU of the Dhaka Hospital of ICDDR,B and many of them present with impending respiratory failure. Children under five with severe pneumonia nearly always have associated severe malnutrition, and many receive mechanical ventilation. This is expensive and is associated with high complication and mortality rates – the death rate was 81% among the **26 children under five who were ventilated due to respiratory failure between January and October, 2010**. There are no published data on the use of bubble-CPAP in children, beyond the newborn period, or in the treatment of pneumonia in developing countries, and no controlled trials of CPAP. We propose to conduct a study to compare the efficacy of (a) bubble CPAP with that of (b) the standard O_2 supplementation by nasal prongs and (c) humidified high flow nasal cannula air / O_2 in the management of hypoxic children with respiratory failure admitted to the ICU of the Dhaka Hospital of ICDDR,B.

Centre's Priority (as per Strategic Plan, to be imported from the attached Separate Word Sheet): 1.3

<table>
<tr><td>Programmes:

☒ Child Health Programme
☒ Nutrition Programme
☒ Programme on Infectious Diseases & Vaccine Science
☒ Poverty and Health Programme
☐ Health and Family Planning Systems Programme</td><td>
☐ Population Programme
☐ Reproductive Health Programme
☐ HIV/AIDS Programme
☐ Gender, Hunman Rights and Health Programme
☐ Others (please specify_____)</td></tr>
<tr><td>Principal Investigator (Should be a Centre's staff)

Mohammod Jobayer Chisti
Address (including e-mail address): Assistant Scientist, Clinical Sciences Division, ICDDR,B
chisti@icddrb.org</td><td>DIVISION:

☒ CSD ☐ LSD
☐ HSID ☐ PHSD</td></tr>
<tr><td colspan="2">Co-Principal Investigator(s): Internal
Mohammed Abdus Salam, Director, CSD, ICDDR,B: E.mail: masalam@icddrb.org
Mark A.C. Pietroni, Medical Director, Dhaka Hospital, ICDDR,B:
E.mail: markp@icddrb.org, Jonathan Harvey Smith, Consultant, ICU, Dhaka Hospital, ICDDR,B:
Consultant Paediatric Anaesthetist, Department ofAnaesthesia, Great Ormond Street Hospital, London, UK. Honorary Senior Lecturer, Portex Unit: PaediatricAnaesthesia, UCL Institute of Child Health, London, UK. E.mail: j.smith@icddrb.org</td></tr>
<tr><td colspan="2">Co-Principal Investigator(s): External:
(Please provide full official address including e-mail address and Gender)

Trevor Duke, Professor and Director, Centre for International Child Health (CICH), The Royal Children's Hospital, Department of Paediatrics, The University of Melbourne
E. mail: trevor.duke@rch.org.au

Stephen M. Graham, Associate Professor, Centre for International Child Health, University of Melbourne Department of Paediatrics; Consultant, Department of Lung Health, International Union Against Tuberculosis and Lung Disease, France; E. mail: steve.graham@rch.org.au</td></tr>
<tr><td colspan="2">Co-Investigator(s): Internal:
Tahmeed Ahmed, Scientist and Head of Nutrition Programme, ICDDR,B; E.mail: tahmeed@icddrb.org
Hasan Ashraf, Scientist, CSD; ICDDR,B; E.mail: ashrafh@icddrb.org
Sharifuzzaman, Medical Officer, EDD, ICDDR,B; E.mail: drsharif@icddrb.org</td></tr>
<tr><td colspan="2">Co-Investigator(s): External
(Please provide full official address including e-mail address and Gender)</td></tr>
<tr><td colspan="2">Student Investigator(s): Internal (Centre's staff):</td></tr>
<tr><td colspan="2">Student Investigator(s): External:
(Please provide full address of educational institution and Gender)</td></tr>
</table>

Collaborating Institute(s): Please Provide full address

Institution # 1

Country	Australia
Contact person	Professor Trevor Duke
Department (including Division, Centre, Unit)	Department of Paediatrics
Institution (with official address)	CICH, The Royal Children's Hospital, The University of Melbourne
Directorate (in case of GoB i.e. DGHS)	
Ministry (in case of GoB)	

Institution # 2

Country	
Contact person	
Department (including Division, Centre, Unit)	
Institution (with official address)	
Directorate (in case of GoB i.e. DGHS)	
Ministry (in case of GoB)	

Institution # 3

Country	
Contact person	
Department (including Division, Centre, Unit)	
Institution (with official address)	
Directorate (in case of GoB i.e. DGHS)	
Ministry (in case of GoB)	

Note: If more than 3 collaborating institutions are involved in the research protocol, additional block(s) can be inserted to mention its/there particular(s).

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

Sex
- ☒ Male
- ☒ Female

Age
- ☒ 0 – 4 years
- ☐ 5 – 10 years
- ☐ 11 – 17 years
- ☐ 18 – 64 years
- ☐ 65 +

- ☐ Pregnant Women
- ☐ Foetuses
- ☐ Prisoners
- ☐ Destitute
- ☐ Service Providers
- ☐ Cognitively Impaired
- ☐ CSW
- ☐ Others (specify)
- ☐ Animal

NOTE It is the policy of the Centre to include men, women, and children in all research projects involving human subjects unless a clear and compelling rationale and justification (e.g. gender specific or inappropriate with respect to the purpose of the research) is there. Justification should be provided in the `Sample Size' section of the protocol in case inclusiveness of study participants is not proposed in the study.

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:

NOTE: Does the study meet the definition of clinical studies/trials given by the International Committee of Medical Journal Editors (ICMJE)? Yes ☒ No ☐

Please note that the ICMJE defined clinical trial as "*Any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome*".

If YES, after approval of the ERC, the PI should complete and send the relevant form to provide required information about the research protocol to the Committee Coordination Secretariat for registration of the study into websites, preferably at the https://register.clinicaltrials.gov/. It may please be noted that the PI would require to provide subsequent updates of the research protocol for updating protocol information in the website.

Targeted Population (Check all that apply):

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

Consent Process (Check all that apply):

☒ Written
☐ Oral
☐ None

☒ Bengali Language
☐ English Language

Proposed Sample Size:

Sub-group (Name of subgroup (e.g. Men, Women) and Number

Name	Number	Name	Number
(1)	975 (325 in each arms)	(3)	
(2)		(4)	

Total sample size: 975

Will the sample(s) be kept for future use? Yes ☐ No NA ☒

If yes, how long the samples be preserved?

Will the consent be obtained from the study participants? Yes ☒ No ☐ NA ☒

What types of tests will be carried out with the preserved samples? _____

Will the samples be shipped to other country(ies)? Yes ☐ No ☒ NA ☒

If yes, name of institution(s) and country(ies): _____

Will the samples be returned to the Centre? Yes ☐ No ☐ NA ☒

Who will be the custodian of the samples? : NA ☒_

Who will be the owner of the samples? : NA ☒_

Has an MOU been made for the protocol? Yes ☐ No ☐ NA ☒

If yes, has copy of the MOU been submitted to IRB? Yes ☐ No ☐ NA ☒

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

☐ Human exposure to radioactive agents?
☐ Foetal 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/sources
☐ Pathological or diagnostic clinical specimen only
☐ Observation of public behaviour
☒ New treatment regime

Yes	No	
☒	☐	Is the information recorded in such a manner that study participants can be identified from information provided directly or through identifiers linked to the study participants?
☐	☒	Does the research deal with sensitive aspects of the study participants' 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:

Yes	No	
☐	☒	Place the study participants at risk of criminal or civil liability?
☐	☒	Damage the study participants' financial standing, reputation or employability, social rejection, lead to stigma, divorce etc.?

Do you consider this research (Check one):

☐ Greater than minimal risk ☒ No more than minimal risk

☐ Only part of the diagnostic test

Minimal Risk is the risk when the probability and magnitude of the anticipated harm or discomfort in participating 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, e.g. 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: (1) Partially funded (Aus$40,000) by the Centre for International Child Health, through a Knowledge Generation Grant from AusAID

(2) The University of Melbourne (scholarships): Aus$22,800/year

Yes/No/NA (if the proposal is already funded, mark NA)
☐ ☒ Is the proposal being submitted for funding?

If yes, name of funding agency: (1)

(2)

Do any of the participating investigators and/or member(s) of 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, a written statement of disclosure to be submitted to the Centre's Executive Director.

Dates of Proposed Period of Support

(Day, Month, Year - DD/MM/YY)

Beginning Date : August, 2011

End Date : July, 2013 (or up to desired sample collection)

Cost Required for the Budget Period ($)

Years	Direct Cost	Indirect Cost	Total Cost
Year-1	57,264		57,26
Year-2	58,442		58,442
Year-3			0
Year-4			0
Year-5			0
Total	1,15,706	0	1,15,706

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 the responsibility for the scientific conduct of the project and to provide the required progress reports including updating protocol information in the SUCHONA (Form # 2) if a grant is awarded as a result of this application.

_____ _____

Signature of PI **Date**

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 reviewers' comments and is approved.

Mohammed Abdus Salam

Name of the Division Director Signature Date of Approval

Table of Contents

☐ Check here if appendix is included

Project Summary

Briefly describe the hypothesis, objectives, and the relevant background of the project, and also 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 should be stand alone, and be fully understandable and interpretable when removed from the main application.

Principal Investigator: Mohammod Jobayer Chisti

Research Protocol Title: Use of bubble CPAP compared to nasal prong oxygen or humidified high flow in children under five with severe pneumonia and hypoxaemia: a randomized trial

Total Budget US$: $US 1,15,706Beginning Date : August, 2011 Ending Date: July, 2013 (or up to desired sample collection)

Continuous Positive Airway Pressure (CPAP) is a common form of support for patients admitted to Intensive Care Units (ICUs) of industrialized countries with respiratory distress (1). Nasal CPAP (NCPAP) is effective in correcting hypoxemia and contributes to reducing the number of children requiring endo-tracheal intubation and mechanical ventilation (2). CPAP is most frequently delivered to neonates using conventional mechanical ventilators, and thus there is minimal or no cost saving. There are other ways of delivering CPAP, such as Bubble-CPAP, which requires a source of gas flow (typically 6–8 L/ minute in a neonate), an air-oxygen blender, a humidifier and a T-piece.(3). The expiratory arm is inserted in a bottle of water and the level of CPAP delivered is equivalent to the length of the expiratory tubing that remains under water. Robust equipment is now available at a fraction of the cost of mechanical ventilators. Bubble-CPAP has potential advantages over the mechanical ventilation, such as lower cost, ease of application by nursing staff, lower risk of complications, and has been proposed as an inexpensive method of delivering CPAP in developing countries (3).

High flow air/ oxygen mix is useful in reducing the indication of mechanical ventilation (4); however, there is a lack of randomized studies comparing it with bubble CPAP or with standard flow O_2 supplementation by nasal prongs. High flow air/oxygen mix uses flows of 2 litre per kg per minute of blended air / oxygen mix, usually with a low fraction of inspired oxygen (say 25-40%). It is easy to apply, but requires additional equipment to standard oxygen therapy, and closer monitoring. "High flow" delivers uncertain levels of CPAP, so it is not clearly superior to bubble-CPAP, and there have been no controlled comparative trials of these two techniques.

Pneumonia and malnutrition are two of the most common co-morbidities in children in developing countries (5). In hospitals in resource-poor settings, children with severe malnutrition and pneumonia often present with respiratory distress with or without severe hypoxaemia and impending respiratory failure (6). They initially receive O_2 supplementation through nasal prong or face mask. Support from bubble CPAP might help to effectively treat hypoxaemia, improve respiratory function, avoid the need for mechanical ventilation and its complications, and reduce mortality.

Almost half of the patients admitted in the intensive care unit of the Dhaka hospital of ICDDR,B present with hypoxaemia, many with impending respiratory failure. Children with pneumonia also invariably have severe malnutrition with or without diarrhoea (Chisti MJ, MMed thesis, unpublished data). They often need mechanical ventilation, with attendant costs, complications and high mortality rates. However, no published data are available about the use of bubble-CPAP in children with pneumonia and malnutrition and there have been no controlled trials of CPAP in developing countries.

The main purpose of our proposed study is to compare the efficacy of (a) bubble CPAP with that of (b) the standard O_2 supplementation by nasal prongs and (c) humidified high flow nasal cannula in the management of hypoxic children with respiratory failure admitted to the ICU of the Dhaka Hospital of ICDDR,B.

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

Name	Professional Discipline/ Specialty	Role in the Project
1. Mohammod Jobayer Chisti	Paediatric respiratory physician	Principal Investigator
2. Mohammed Abdus Salam	Internist	Co-PI
3. Mark A. C. Pietroni	Medicine specialist/Pulmonologist	Co-PI
4. Jonathon Smith	Paediatrician Anaesthetist/Intensive care specialist	Co-PI
5. Trevor Duke	Paediatrician/Intensive care specialist	Co-PI
6. Stephen Graham	Paediatrician	Co-PI
7. Tahmeed Ahmed	Nutritionist and Epidemiologist	Co-I
8. Hasan Ashraf	Internist/Paediatrician	Co-I
9. Sharifuzzaman	Internist	Co-I

Description of the Research Project

Hypothesis to be Tested:

Please briefly list the Hypothesis to be tested and provide the scientific basis of the hypothesis, critically examining the observations leading to the formulation of the hypothesis.

On the basis of the above background, our primary hypothesis is that:

1. In children with severe pneumonia and hypoxaemia the probability of treatment failure (see definition below) will be significantly lower when respiratory support is initially provided by bubble-CPAP compared to standard nasal prong O_2 and humidified high flow for children with severe pneumonia and hypoxaemia.

Our secondary outcomes are:

2. Mortality rate at hospital discharge, rate of need for mechanical ventilation, rates of nosocomial infections (if clinical features of new episode of infection develops 48-72 hours after admission to a hospital), rates of multi-organ failure at 7 days, length of hospital stay, rate of absconding, bacterial aetiology and rates of isolation of TB will be significantly different when treatment is provided by bubble-CPAP, compared to standard nasal prong O_2 and humidified high flow for children with severe pneumonia and hypoxaemia

Specific Aims:

Describe the specific aims of the proposed study. State the specific parameters, biological functions, rates, processes etc. that will be assessed by specific methods.

The specific objectives of the study are:

Primary objective:

To evaluate the rates of treatment failure (see definition below) in neonates and children with severe pneumonia and hypoxaemia treated by bubble-CPAP, humidified high flow (2 litres per kg per min) air / O_2 mix by nasal cannula, and standard treatment using only oxygen (0.5 – 2 litres per min) via nasal cannula.

Secondary objectives:

To evaluate complication rates, such as mortality rate at hospital discharge, rate of need for mechanical ventilation, rates of nosocomial infections (new infection occurs at least 48 hours after admission or at least 48 hours after complete resolution of treated infection at hospital and new infection will be featured with newly appeared clinical signs), rates of multi-organ failure (more than one organ failure such as renal failure and respiratory failure in addition to clinical evidence of septic shock), length of hospital stay, and rate of absconding among neonates and children with severe pneumonia and hypoxaemia when managed by bubble-CPAP, compared to high-flow, humidified oxy-therapy and standard low flow oxygen therapy.

Background of the Project including Preliminary Observations

Provide relevant background of the proposed study, and discuss the previous works on the research topic by citing specific references. Describe in a logical way how the present hypothesis is supported by the relevant background observations including any preliminary results that may be available. Provide scientific validity of the hypothesis on the basis of background information 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.. 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.

Despite the availability of basic care, including appropriate antimicrobial therapy and oxygen therapy, case fatality rates (CFR) for childhood pneumonia, especially among severely malnourished, remain high in developing countries(5). While CFR in severe pneumonia in well nourished children can be as low as 3-5% with good quality care (7), it can be as high as 20% or even greater in hypoxic, severely malnourished children (8). The causes of this differential CFR is multifactorial and includes different bacterial epidemiology, co-existent disease (such as diarrhoea and dehydration) and muscle weakness leading to respiratory failure (5, 6). In the management of hypoxaemia in such children standard oxygen therapy alone might not be adequate. Continuous Positive Airway Pressure (CPAP) may improve survival rates by provide additional respiratory support (9). Among premature newborns in developing countries, low birth weight and sepsis associated with hypoxaemia, apnoea and respiratory failure are common complications and are associated with high CFR (10-12). By supporting respiration and reducing the need for high concentration oxygen, CPAP might also reduce the risk of retinopathy due to oxygen toxicity (13).

The provision for advanced, high-end respiratory support, associated with high cost, is difficult to establish and not a priority in resource-poor settings where infectious diseases including pneumonia remains the leading cause of death. Equipment costs, training, and higher salaries of ICU staff are among major constrains in establishing such facilities, where funding for Western style intensive care would better be spent on public health initiatives or improving basic quality of care. In industrialized countries mechanical ventilation remains the cornerstone of intensive care, which is frequently associated with high mortality from complications (e.g. procedural errors, nosocomial infections, inadequate monitoring, late initiation of ventilation) in developing countries (1). Setting up of an appropriate, low technology-and low-cost model of referral-level intensive care is necessary in developing countries.

In the industrialized countries, CPAP is now a common form of support for patients with respiratory distress admitted to ICU units (1). It works by maintaining a positive pressure in the airway during spontaneous breathing, results in opening of the collapsed alveoli, lessening intrapulmonary shunts, and increasing functional residual capacity, which helps correct

hypoxaemia and may reduce the number of children requiring endo-tracheal intubation and mechanical ventilation (14). CPAP is most frequently delivered to neonates using conventional mechanical ventilators, which is associated with higher costs. There are other ways of delivering CPAP, such as Bubble-CPAP, which requires a source of gas flow (typically 6–8 L per minute for a neonate), an air-oxygen blender, a humidifier and a T-piece, and its expiratory arm is dipped into a bottle of water (3). The CPAP can be delivered either by helmet or facial masks or nasal canulas, and level delivered is equivalent to the length of the expiratory tube in water. NCPAP delivered by helmet has been reported to improve oxygenation better than that of facial musks and nasal canulas in young infants and older children (15). Robust equipment is currently available at a fraction of the cost of mechanical ventilators. Bubble-CPAP has several potential advantages over mechanical ventilation, such as lower cost, application by nursing staff and lower risk of complications, and has been proposed as an inexpensive and feasible method of delivering CPAP in developing countries (3).

High flow O_2 supplementation, such as using Bubble-CPAP, is useful in reduce the need for mechanical ventilation (4). However, there is no randomized study to compare the efficacy of mechanical with Bubble-CPAP or with delivery of O_2 by nasal prongs.

Nearly half of the patients admitted to the ICU of the Dhaka Hospital of ICDDR,B present with hypoxaemia, and many of them with impending respiratory failure. Children with pneumonia seen at this facility almost invariably have severe malnutrition (Chisti MJ, MMed thesis, unpublished data). At this unit, children with pneumonia and hypoxaemia are initially managed with O_2 supplementation. Introduction of Bubble-CPAP at this hospital might help improve respiratory functions of greater proportion of children without the use of mechanical ventilation and thereby reduce its complications, and reduce hospital costs and mortality (14).

The main purpose of our proposed study is to compare the efficacy of (a) bubble CPAP with that of (b) the standard O_2 supplementation by nasal prongs and (c) humidified high flow nasal cannula in the management of hypoxic children with respiratory failure admitted to the ICU of the Dhaka Hospital of ICDDR,B.

Research Design and Methods

Describe in detail the methods and procedures to be used in accomplishing 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.

1. Design and Methods

1.1 Study design: This will be a randomised, controlled study in which we will prospectively provide intervention in children under the age of 5 years admitted to the Dhaka Hospital of ICDDR,B and fulfilling the inclusion criteria (January 2011 and December 2012), subject to the obtaining written informed consent from respective parents/care-givers.

1.2 Eligibility Criteria

1.2.1 Inclusion criteria: Children of either sex, aged 0-4 years, with severe/very severe pneumonia (per WHO guidelines) and hypoxaemia (SpO_2 < 90%) will be included in our study in the ARI Unit of the Longer Stay Ward (LSW), High Dependency Unit HDU, and ICU unit of Dhaka Hospital of ICDDR,B.

1.2.2 Exclusion criteria: Children with uncorrected cyanotic CHD, hypercapnoea (PCO_2 > 60mm of Hg), status asthmaticus and upper-airway obstruction, preterm baby (but not ex-preterm), and those for whom inform consent can't be secured from their parents/ care-givers. Children with features (any two of three criteria given below) of "clinical failure" on admission (before enrolment into the study) will also be excluded from the study. Arterial blood gas analysis will be performed to check the exclusion criteria.

1.3 Intervention and comparators

Children under five admitted to the SCU of ICDDR, B with pneumonia and hypoxaemia will be studied. This study will evaluate the proportions of deaths in children under five in three treatment arms.

We will use sealed envelopes to randomly assign the children to one of three treatment arms. In first arm, children will receive bubble CPAP (bubble CPAP pressure of 5 to 10 cm of H2O); in 2nd arm, children will receive standard O_2 supplementation by nasal cannula at 0.5 – 2 L/min (or 4l/min for children > 2 years); in the 3rd arm, children will receive humidified high flow air / O_2 mix at 2 L/kg/min (maximum 12L/min) through nasal cannula from a high flow generator. The three arms will be compared for rates of treatment failure (see below).

During the study period, children (whether under ventilation or not) in all three study arms will also receive standardized hospital management for pneumonia and malnutrition.

"Treatment failure" will be standardized, based on clinical and monitoring data.

During the study period any child from either study group who develops the features of "clinical failure" (any two of three criteria in the definition below) will be managed according to best practice in the clinical context. If children fail the arm of standard 2L nasal cannula O_2 they should be rescued with B-CPAP or humidified high flow air / O_2 mix at 2 l/kg/min through nasal cannula after further randomization. However, if children fail the arms of humidified high flow air / O_2 mix at 2 l/kg/min or bubble CPAP, they will receive mechanical ventilation. "Clinical failure" is the criteria to be followed to decide intubation and mechanical ventilation.

Laboratory investigations:

Routine: Blood (5.0 ml) for total and differential count of white blood cell (WBC), haematocrit, culture and sensitivity, serum electrolytes and creatinine, stool culture and urine culture, chest radiograph (CXR) on admission. Venipuncture for blood culture collection was performed by the attending physician under aseptic precautions. The puncture site was disinfected using two agents (10% povidone iodine followed by 70% rectified spirit) and left to dry for 30 to 60 seconds. 2.0 mL of blood was collected and injected into standard pediatric blood culture bottles and sent to our icddr,b microbiology laboratory where it used to be processed for the culture and sensitivity following standard procedure.

Protocol-specific: Arterial blood gas analysis, tuberculin skin test (TST), gastric lavage for acid fast bacilli (AFB) and culture for MTB.

1.4 Measurements

All children will be monitored for by pulse oximetry for arterial O_2 saturation, respiratory rate, lower chest wall in-drawing, intercostal retraction, head nodding, cyanosis, tracheal tug, heart failure (defined by the presence of tachypnea, tachycardia, gallop rhythm, hepatomegaly, pedal oedema, basal crackles). Pulse oximetrty monitoring is the most accurate non-invasive and real time measurement of respiratory status, which along with clinical signs will be the main method of monitoring. Arterial or capillary blood gas analyses will be done for children failing to maintain saturation (≥90% with allocated treatment), or if there is concern about hypercarbia or acidosis.

1.5 Criteria for primary outcome: Treatment failure

The primary outcome (treatment failure), by intention to treat analysis will be reached if a child:

A. Has **any two or more** of the following three criteria of clinical failure (after at least half an hour of intervention)

1. Severe hypoxaemia (SpO_2<85%) after being on one of the study arm treatments for >^{1}/2 hour
2. Clinical signs of severe respiratory distress, including moderate-severe chest wall in-drawing, tracheal tug, nasal flaring or grunting respirations
3. PCO_2 >60mm Hg and pH<7.2 on capillary blood gas OR

B. Receives intubation and / or mechanical ventilation OR

C. Dies while in hospital or within 30 days of discharge OR

D. Left against medical advice * while still on the allocated respiratory support.
* If they abscond the day before they are due to be discharged and they are off oxygen and are well, then that's just a mother's choice to go home early, such children should not be put in the category of equivalent of treatment failure.

2 Sample Size Calculation and Outcome (Primary and Secondary) Variable(s)

Background, recent data (1st January until 31st October, 2010) from the ICU of the Dhaka Hospital of the ICDDR,B revealed that the approximate treatment failure from the management of hypoxaemia in children with pneumonia and severe malnutrition was 30%. We assumed that the new intervention would result in a reduction of treatment failure from 30% to 18% (i.e. a 40% absolute reduction). Thus to detect a difference of 40% in the death from hypoxaemia with 90% power and type 1 error 0.03 (we are intending to do interim analysis and for that we are considering type 1 error 0.03 instead of 0.05), the sample would be 295 children in each group {sample size = $[(p_1 \times q_1 + p_2 q_2)/ (p_2 - p_1)^2] \times$factor for α, β; where is the p_1 is the percentage of the "treatment failure", q_1 is the 1- p_1, p_2 is the percentage of the expected "treatment failure" from intervention; q_2 is the 1- p_2, α is the type 1 error and β is the type 2 error and factor for α, β with 90% power is 11.9}. Considering 10% drop out after admission in hospital, the total sample size is at least 325 in each group. So, our total sample size will be 325×3=975. The patients will be enrolled over a period of two years.

Facilities Available

Describe the availability of physical facilities at site of conduction of the study. For clinical and laboratory-based studies, indicate the provision of hospital and other types of adequate patient care and laboratory support services. Identify 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.

This study will be conducted at the Dhaka Hospital of ICDDR,B, Dhaka, Bangladesh. This hospital is located in Dhaka city, the capital of Bangladesh. It provides care and treatment to around 110,000 diarrheal patients with or without associated complications and with or without other health problems each year. The vast majority of the patients come from poor socio-economic backgrounds from urban and peri-urban Dhaka, the capital city of Bangladesh.

Patients attending this hospital are first assessed by an experienced triage nurse, which include assessment of the type of diarrhoea and degree of dehydration, and presence of other health problems including ALRI/ pneumonia, severe malnutrition, impaired mental status (convulsion), and sepsis. They redirect non-diarrhoeal patients to other appropriate city hospitals in the city. Based on assessment of diarrhoeal patients, those with uncomplicated illness without signs of dehydration are referred to the Out Patient Unit for 1-2 hours of observation, maintenance of hydration using ORS solution, and for provision of health education to the mothers/caregivers. Those with some and severe dehydration but without any associated health problems are admitted to Short Stay Ward (SSW) for correction of dehydration and maintenance of hydration using ORS and/or intravenous fluids, provision of antimicrobial therapy as appropriate, with an average stay of 24 hours. Those with associated complications of diarrhoea and/or associated health problems are referred to a physician for assessing the need for admission to either the Longer Stay Ward (LSW) or Acute Respiratory Ward (ARI) or to the Special Care Word (SCU) depending on the clinical severity. The usual associated conditions include difficult respiration, cyanosis, apnoea, hypothermia or hyperthermia, marked lethargy or comatose condition, poor peripheral perfusion not attributable to severe dehydration. Those hospitalised in SSW for 120 hours are assessed by hospital clinicians for possible admission to LSW and further workup and management. After admission to the LSW/ARI/SCU the attending physician obtained medical history, performs thorough clinical examination, makes a problem list including differential diagnoses for each of them, arranges for required laboratory workups, and develops the treatment plan following standard guidelines of the hospital. They also perform bedside procedures such as sampling blood, performing lumber puncture etc. Oxygen saturation is determined by pulse oximeter when necessary, and blood glucose estimated by bedside Glucocheck machine in nearly all patients admitted to the LSW/ARI /SCU.

Respiratory ward Infrastructure:

An independent acute respiratory infection treatment unit was established right at the entrance to the hospital, and started functioning on 6 September, 2009. Patients reporting to Dhaka Hospital were rapidly screened for respiratory symptoms such as fever, cough, myalgia, headache, chills, fatigue, running nose, sore throat, rapid breathing and difficulty in breathing. Patients with these symptoms were referred to the respiratory triage where they were assessed following the hospital guidelines and relevant information was entered into the hospital's electronic database. Patients with any form of pneumonia (non-severe, severe, and very severe), bronchiolitis, asthma, bronchitis, pleural effusion, empyema, lung abscess, tuberculosis, and any other common respiratory problems are admitted in the ward. Others were referred to the usual diarrhoea triage of the hospital. Sufficient staff provide 24 hour cover from all cadres (doctors, nurses, health workers and auxiliary staff). This facility was provided with all necessary supplies including a portable X-ray machine, Ambu bags, large oxygen cylinders, pulse oxymeters, disposable gloves, disinfectants and medication (e.g. antibiotics and other medicines). Pulse oximetry is routinely performed to

evaluate arterial oxygen saturation, and additional tests were performed if there were clinical indications. Vital signs were monitored, and stool and urine output was measured and recorded 8 hourly. Therapy is decided on the basis of clinical evaluation, results of the laboratory tests, and the hospital guidelines for management of respective respiratory illness.

Data Safety Monitoring Plan (DSMP)

All clinical investigations (biomedical and behavioural intervention research protocols) should include the Data and Safety Monitoring Plan (DSMP) to provide the overall framework for the research protocol's data and safety monitoring. It is not necessary that the DSMP covers all possible aspects of each element. When designing an appropriate DSMP, the following should be kept in mind.

a) All investigations require monitoring;
b) The benefits of the investigation should outweigh the risks;
c) The monitoring plan should commensurate with risk; and
d) Monitoring should be with the size and complexity of the investigation.

Safety monitoring is defined as any process during clinical trails that involves the review of accumulated outcome data for groups of patients to determine if any treatment procedure practiced should be altered or not.

Data safety Monitoring will be rigorously performed throughout the course of the study mainly by an independent DSMB who will visit randomly to review the forms for completeness, legibility, and internal consistency. This trial has a formally constituted DSMB. This DSMB consists of senior scientists from Icddr,b, many who are independent of the trial, some of whom also sit on the icddr,b's Ethics Research Committee. Other members of the DSMB for this study include Prof Trevor Duke from the University of Melbourne. The DSMB will meet every 6 months and if they feel the necessity they may evaluate data on all components of the composite primary outcome, and all adverse events. If there are any differences in the primary outcome or the adverse events that are not included in the primary outcome between the three groups, the trial will be stopped. Icddr,b's ERC required reporting of all serious adverse events (SAE) within 24 hours; for this study all adverse events (AE) will also be reported by the study investigators to the DSMB within 24 hours of their occurrences using a standard case reporting form. As this is an open trial the implications of an adverse event can be better interpreted throughout the conduct of the trial than would be possible if any blinding was involved. The DSMB will have full access to all case reporting forms and trial data, not only every 6 months, but whenever it is appropriate if there are any concerns over excess adverse events or unbalanced events between the three study groups. All aspects of intervention and interpretation will be performed according to rigorously standardized standards of procedures (SOPs).

Data Analysis

Describe plans for data analysis. Indicate whether data will be analysed 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 determine further course of the study.

Questionnaires will be visually scanned soon after interview and marked for omissions, inconsistencies or mistakes that will be addressed immediately. Data will be entered into a personal computer using Statistical Package for Social Sciences, version 12.0 Windows, (SPSS, Chicago, IL) after creating a template for each data entry file with appropriate logical and consistency

checks. Data will be continuously entered as it is being generated in hospital, laboratory, and field. All data will be entered a second time, then consistency between two will be verified by matching with detected errors then necessary corrections will be made. In addition, data will be validated by a series of logical and range checks, producing summary statistics and tables. Data will be immediately copied on the hard disks of two computers as soon as data verification is complete.

Data analysis will be performed using the SPSS, version 12.0 Windows, (SPSS, Chicago, IL) and Epi Info (version 6.0, USD, Stone Mountain, GA). Data will be summarized and findings of one site will be compared with that of other sites(s). Statistical analyses will include descriptive as well as analytical methods. When the variable of interest is a categorical variable, the significance of differences will be evaluated by chi-square test or Fisher exact test. When the main outcome measures are continuous variables, the statistical significance of two groups (bubble CPAP vs. standard low flow or humidified high flow) will be determined by students "t" test or Mann-Whitney test as appropriate. A probability of less than 0.05 will be considered statistically significant except primary outcome (probability of less than 0.03 will be considered statistically significant for primary outcome). Strength of association will be determined by calculating odds ratio (OR) and 95% confidence intervals (CI). Finally, regression analyses will be performed for more definitive conclusions where treatment failure will be the dependent variable and factors associated with treatment failure by univariate analysis will be independent variables. Regression analyses will also be performed to evaluate independent predictors for death where deaths will be the dependent variable and factors associated with deaths in our study population by univariate analysis will be independent variables.
.

We are intending to perform an interim analysis of the data to see any significant difference among the treatment arms. If one of the three treatment arms will show any significant beneficial effect, we will inform the ERC and simultaneously stop the study without any further delay due to ethical obligation and implement the best treatment modality of oxygen delivery for the hospital patients.

After the completion of the analysis, important results will be incorporated to the national pneumonia guideline. It is prudent to mention that the children who will be "absconded" from our study after randomization due to any reason will also be included in our primary analysis and will be considered them as INTENTION TO TREAT (ITT) ANALYSIS. Thus, ITT analysis should be, any child who, after randomization:

- Fulfils the criteria for treatment failure as defined in the proposal
  OR
- Receives intubation and / or mechanical ventilation
  OR
- Dies
  OR
- Left against medical advice while still on the allocated respiratory support

Outcome variables

1. The primary outcome will be treatment failure (see definition above).
2. The secondary outcomes will be:
    a. Mortality rate calculated at hospital discharge
    b. Rate of need for mechanical ventilation
    c. Rates of nosocomial infections
    d. Rates of multi-organ failure at 7 days
    e. Length of hospital stay

f. Rate of absconding
g. Bacterial aetiology
h. Rates of isolation of TB

Ethical Assurance for Protection of Human Rights

Describe the justifications for conducting this research in human participants. If the study needs observations on sick individuals, provide sufficient reasons for using them. Indicate how participants rights will be protected, and if there would be benefit or risk to each participants of the study.

The study will be performed in compliance with the 'Declaration of Helsinki' (2000), the International Conference of Harmonization (ICH), Tripartite Guidelines, Guideline for Good Clinical Practice (GCP). These procedures ensure the protection of the rights and the integrity of the study participants, adequate and correct conduct of all study procedures, adequate data collection, adequate documentation and adequate data verification.

The study will only be initiated after it has been approved by the Research Review Committee (RRC) and the Ethical Review Committee (ERC) of ICDDR,B. Before enrolment signed informed consent will be obtained from the adults and from the parents/guardians of the children. The consent form will be written in Bangla in a language and format that will be easily understood by the study subject of even little or no educational background. The consent form will be read out to the care-giver/legal guardian/parent of the study subject if he/she is unable to read. Signed consent or the left thumb impression will be obtained from the care-giver/legal guardian/parent for participation of the children in the study. Consent will be taken both for participation in the study and collecting samples as outlined in the different aims (Consent forms in appendices 5a, b and c).

Use of Animals

Describe if and the type and species of animals to 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 does not involve use of animals

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.

Please see the reference list

Dissemination and Use of Findings

Describe explicitly the plans for disseminating the accomplished results. Describe if and how the research findings would be shared with stakeholder, identifying them if known, and the mechanism to be used. Also describe what type

of publication is anticipated: working papers, internal (institutional) publication, international publications, international conferences and agencies, workshops etc. Indicate, if the project is linked to the Government of the People's Republic of Bangladesh through a training programme or a collaborative arrangement.

We hope that this study will explore to a better understanding of the compared usefulness of the bubble CPAP, and humidified high flow air / oxygen mix by nasal canula among children with severe pneumonia and hypoxaemia. This study should enable better models of high dependency intensive care to be developed in resource limited countries, and avoid excessive money being spent on Western style intensive care units. We will share the information with policy makers to create awareness about the compared usefulness of the bubble CPAP, standard oxygen therapy and humidified high flow by nasal canula for these children in Bangladesh**.**

The results of the study will be disseminated in several ways: (i**) this will use to defend the thesis of PhD for principal investigator (Mohammod Jobayer Chisti) at the University of Melbourne**. (ii) The findings of the study will be disseminated through workshops and conferences at national and international level. Moreover, results will be published in reputed national, regional, and international journals.

Collaborative Arrangements

Briefly describe 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.

This study is a collaborative effort of researchers from the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) and the Centre for International Child Health (CICH), the Royal Children`s Hospital, the Department of Paediatrics, the University Melbourne.
Data analysis, interpretation, and publication will be done in close collaboration of the partners.

Institutional contracts will define the roles and responsibilities of each institution according to the following lines:

ICDDR, B:
Will provide research infrastructure, personnel, and conduct study in Bangladesh, plus co-supervision.

Centre for International Child Health, The Royal Children's Hospital, Department of Paediatrics, The University Melbourne:
Provides technical assistance, and co-supervision of PhD of the PI, and assistance with funding.

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.

(Note: Biography of the external Investigators may, however, be submitted in the format as convenient to them)

1 Name: Mohammod Jobayer Chisti

2 Present Position: Assistant Scientist, CSD, ICDDR,B, Dhaka, Bangladesh.

3 Educational background:
(last degree and diploma & training

Masters in Medicine (MMed) (Paediatrics), The Royal Children`s Hospital, The Department of Paediatrics, The University of Melbourne, Melbourne, Australia, 2010
Received one year (March`2008 - February`2009) training in General Paediatrics and Paediatric Intensive Care Unit, and one year (March`2009 - February`2010) advance training in Paediatric Respiratory Medicine, The Royal Children`s Hospital, The Department of Paediatrics, The University of Melbourne, Melbourne, Australia

4.0 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

5 Publications

Types of publications	Numbers
a. Original scientific papers in peer-review journals	53
b. Peer reviewed articles and book chapters	4
c. Papers in conference proceedings	38
d. Letters, editorials, annotations, and abstracts in peer-reviewed journals	1
e. Working papers	4
f. Monographs	1

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

1. Chisti MJ, Salam MA, Bardhan PK, Sharifuzzaman, Ahad R, Vincente S La and Duke T. Influences of dehydration on clinical features of radiological pneumonia in children attending an urban diarrhoea treatment centre in Bangladesh. *Annals of Tropical Paediatrics* 2010; 30: 311-316

2. **Chisti MJ**, Ahmed T, Faruque ASG and Salam MA. Clinical and laboratory features of radiologic pneumonia in severely malnourished infants attending an urban diarrhea treatment center in Bangladesh. *Pediatric Infectious Disease Journal* 2010; 29: 174-77

3. **Chisti MJ**, Salam MA, Sharifuzzaman, and Pietroni MAC. Occult Pneumonia: An Unusual but Perilous Entity Presenting with Severe Malnutrition and Dehydrating Diarrhoea. *Journal of Health, Population and Nutrition* 2009; 27: 808-812

4. **Chisti MJ,** Tebruegge M, Vincente S La, Graham SM and Duke T. Pneumonia in severely malnourished children in developing countries: mortality risk, aetiology and validity of WHO clinical signs: a systematic review. *Tropical Medicine and International Health* 2009; 14: 1173-1189

5. Ahmed T, Sobhan F, Ahmed AMS, Banu S, Mahmood AM, Hyder KA, **Chisti MJ**, Abdullah K, Mahfuz M, Salam MA. Childhood Tuberculosis: a Review of Epidemiology, Diagnosis and Management. *Infectious Diseases Journal of Pakistan* 2008; 17: 52-60

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.

(Note: Biography of the external Investigators may, however, be submitted in the format as convenient to them)

Trevor David Duke, MB BS MD FRACP FJFICM

Current position	Professor and Director Centre for International Child Health University of Melbourne Royal Children's Hospital Victoria, 3052 Australia
Other appointments	Director, World Health Organization Collaborating Centre for Research & Training in Child & Neonatal Health
	Intensive Care Specialist, Royal Children's Hospital, Melbourne
	Adjunct Professor of Child Health, School of Medicine & Health Sciences, University of Papua New Guinea
Date of Birth	4th August 1963
E-mail	trevor.duke@rch.org.au
Telephone	Office: (613) 9345 5968, Switch: (613) 9345 5522 (page 5968)
Place of birth:	Victoria, Australia Nationality: Australian

MEMBERSHIP OF PROFESSIONAL ASSOCIATIONS

Royal Australasian College of Physicians (1996-)

Chairman, Asia-Pacific Committee, Royal Australasian College of Physicians (2001-)

Joint Faculty of Intensive Care, Royal Australasian College of Physicians / Anaesthetists (2002-)

Papua New Guinea Paediatric Society (1997-)

Medical Society of Papua New Guinea (1997-)

RESEARCH FOCUS: Reducing child and neonatal mortality in developing countries, pneumonia, quality of paediatric care, oxygen therapy, research capacity development

POST GRADUATE EXAMINATIONS / QUALIFICATIONS

1993 FRACP examination

1996 Fellowship of the Royal Australasian College of Physicians

8 Doctorate of Medicine, University of Melbourne

The Centre for International Child Health is the only World Health Organization Collaborating Centre for Research and Training in Child and Neonatal Health in Australia. The Centre is part of the AusAID Women's and Children's Health Knowledge Hub, a new initiative established by AusAID in 2008 to support the contribution of Australian academic institutions to health in the Asia and Pacific regions.

PUBLICATION SUMMARY

- Refereed original research articles 66
- Reviews 20
- Invited commentaries or editorials 18
- Book chapters 7
- Presentations at scientific meetings 53
- Editorial Board: Journal of Paediatrics and Child Health and Annals of Tropical Paediatrics Child Health in Papua New Guinea
- Adjunct Professor of Child Health, School of Medicine & Health Sciences, UPNG since 2004 (visiting Lecturer since 2001)
- Member, PNG National Department of Health Child Health Advisory Committee
- Paediatrician, Goroka Base Hospital, Papua New Guinea 1997-2001

RESEARCH AND OTHER GRANTS

Year	Investigators	Nature of grant	Amount
2008-2011	Duke T, Carapetis J, Holmes W	AusAID Knowledge Hub for Women's and Children's Health	$2 million per year for 3 years
2005-2008	Duke T, WHO Collaborating Centre for Research and Training in Child and Neonatal Health	Contracts for various projects in the region and global initiatives, through World Health Organization	>$250,000 between 2005-10
2006-2010	Duke T	RE Ross Trust, PNG Research and Leadership Scholarship	$87,000 per year from 2006-10
2008	Duke T, Subhi R	Knowledge Transfer Grant, University of Melbourne	$10,000
2003	Duke T	2003. University of Melbourne. Early Career Research Development Grant	$36,000

		Effect of improving oxygen systems on mortality in rural hospitals in developing country ($36,000)	
1996	Duke T	The Royal Australasian College of Physicians' Cottrell Fellowship Research Project: Fluid management of bacterial meningitis ($20,000)	$20,000
1995-6	Duke T	Trainee Research Scholarship, RCH Research Foundation: Cardiovascular monitoring of critically ill children ($44,000)	$44,000

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

1. **Duke T**, Wandi F, Jonathan M, Matai S, Subhi R, Peel D. Impact of improved oxygen systems on child deaths from pneumonia: a multi-hospital effectiveness study in Papua New Guinea **Lancet** 2008; 372:1328-1333
2. Subhi R, Adamson M, Campbell H, Weber M, Smith K, **Duke T** and the Global Hypoxaemia Prevalence Study Group. The prevalence of hypoxaemia among ill children in developing countries: a systematic review. **Lancet Infectious Diseases** 2009.
3. Chisti MJ, Tebruegge M, La Vincente S, Graham SM, **Duke T**. Pneumonia in severely malnourished children in developing countries: mortality risk, aetiology and validity of WHO clinical signs: a systematic review. *Tropical Medicine and International Health* 2009; 14: 1173-1189
4. **Duke T**, Graham SM, Cherian MN, Ginsberg AS, English M, Howie S, Peel D, Enarson PM, Wilson IH, Were W; the IUATLD Oxygen Systems Working Group Oxygen is an essential medicine: a call for international action.. *Int J Tuberc Lung Dis* 2010; 14: 1362-1368
5. **Duke** T, Peel D, Graham S, Howie S, Enarson PM, Jacobson R. Oxygen concentrators: a practical guide for clinicians and technicians in developing countries. Ann Trop Paediatr. 2010;30(2):87-101.
6. Theodoratou E, Al-Jilaihawi S, Woodward F, Ferguson J, Jhass A, Balliet M, Kolcic I, Sadruddin S, **Duke T**, Rudan I, Campbell H.The effect of case management on childhood pneumonia mortality in developing countries. Int J Epidemiol. 2010 Apr;39 Suppl 1:i155-71.

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.

(Note: Biography of the external Investigators may, however, be submitted in the format as convenient to them)

1 Name: Stephen Michael Graham

2 Present Position: Associate Professor, Centre for International Child Health, University of Melbourne Department of Paediatrics, Melbourne, Australia

3 Educational background:

(last degree and diploma & training relevant to the present research proposal)

PhD, University of Amsterdam
Diploma in Tropical Child Health, University of Liverpool
Fellow of the Royal Australasian College of Physicians

4.0 List of ongoing research protocols

(start and end dates; and percentage of time)

4.3 As Co-Investigator

Protocol Number	Starting date	End date	Percentage of time

5 Publications

Types of publications	Numbers
a. Original scientific papers in peer-review journals	69
b. Peer reviewed articles and book chapters	46
c. Papers in conference proceedings	15
d. Letters, editorials, annotations, and abstracts in peer-reviewed journals	15
e. Working papers	0
f. Monographs	15

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

1. Duke T, **Graham SM**, Cherian MN, Ginsberg AS, English M, Howie S, Peel D, Enarson PM, Wilson IH, Were W; the IUATLD Oxygen Systems Working Group Oxygen is an essential medicine: a call for international action.. *Int J Tuberc Lung Dis* 2010; 14: 1362-1368
2. **Graham SM**. Research into tuberculosis diagnosis in children. *Lancet Infect Dis* 2010; 10: 581-582
3. **Graham SM**, Mankhambo L, Phiri A, Kaunda S, Chikaonda T, Mukaka M, Molyneux EM, Carrol ED, Molyneux ME. Impact of human immunodeficiency virus infection on etiology and outcome of severe pneumonia in Malawian children. *Pediatr Infect Dis J* 2010 (in press)
4. Enarson PM, Gie RP, Enarson DA, Mwansambo C, **Graham SM**. The impact of HIV on standard case management for the inpatient treatment of childhood pneumonia in high HIV prevalence countries. *Expert Rev Resp Med* 2010; 4: 211-220
5. Chisti MJ, Tebruegge M, La Vincente S, **Graham SM**, Duke T. Pneumonia in severely malnourished children in developing countries: mortality risk, aetiology and validity of WHO

clinical signs: a systematic review. *Tropical Medicine and International Health* 2009; 14: 1173-1189

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.

(Note: Biography of the external Investigators may, however, be submitted in the format as convenient to them)

1. **Name** : Mohammed Abdus Salam

2. **Present position:** : Director, Clinical Sciences Division, ICDDR,B.

3. **Educational background:** MBBS: from the Dhaka Medical College
(last degree and diploma & training relevant to the present research proposal) University of Dhaka, Bangladesh

4. **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

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

5 Publications

Types of publications	Numbers
a. Original scientific papers in peer-review journals	Over 100
b. Peer reviewed articles and book chapters	4
c. Papers in conference proceedings	Appx. 50
d. Letters, editorials, annotations, and abstracts in peer-reviewed journals	1

e. Working papers	
f. Monographs	

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

6.1 M. J. Chisti, **M. A. Salam**, P. K. Bardhan, Sharifuzzaman, R. Ahad, S. La Vincente and T. Duke. Influences of dehydration on clinical features of radiological pneumonia in children attending an urban diarrhoea treatment centre in Bangladesh. *Annals of Tropical Paediatrics* 2010; 30: 311-316

6.2 Chisti MJ, Saha S, Roy CN, **Salam MA**. Predictors of bacteremia in infants with diarrhea and systemic inflammatory response syndrome attending an urban diarrheal treatment center in a developing country. Pediatr Crit Care Med. 2010 Jan;11(1):92-7.PMID: 19593244

6.3 Chisti MJ, Ahmed T, Faruque AS, Saha S, **Salam MA**, Islam S. Factors associated with sclerema in infants with diarrhoeal disease: a matched case-control study. Acta Paediatr. 2009; 98: 873-878

6.4 Ashraf H, Jahan SA, Alam NH, Mahmud R, Kamal SM, **Salam MA**, Gyr N. Day-care management of severe and very severe pneumonia, without associated co-morbidities such as severe malnutrition, in an urban health clinic in Dhaka, Bangladesh. Arch Dis Child. 2008 Jun;93(6):490-4. Epub 2007 Sep 5.

6.5 Ashraf H, Jahan SA, Alam NH, Mahmud R, Kamal SM, **Salam MA**, Gyr N. Day-care management of severe and very severe pneumonia without any associated co-morbidities like severe malnutrition in an urban health clinic in Dhaka, Bangladesh. Arch Dis Child. 2007 Sep 5; [Epub ahead of print]

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.

(Note: Biography of the external Investigators may, however, be submitted in the format as convenient to them)

1 Name: Mark Arthur Charles Pietroni

2 Present Position: Administrator and Consultant, Dhaka Hospital, ICDDR,B

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

MBBS; MRCP
Pulmonologist

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

4.2. As Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

4.3. As Co-Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

4.4. As Co-Investigator

Protocol Number	Starting date	End date	Percentage of time

5 Publications

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

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

1. Chowdhury F, Chisti MJ, Khan AH, Chowdhury MA, **Pietroni M**A. Salmonella Typhi and Plasmodium falciparum co-infection in a 12-year old girl with haemoglobin E trait from a non-malarious area in Bangladesh. J Health Popul Nutr. 2010 Oct;28: 529-31.

2. **Pietroni M**, Azim T. The growing need for service provision for people living with HIV in Bangladesh. J Health Popul Nutr. 2010;28: 209-10.

3. Chisti MJ, Salam MA, Sharifuzzaman, **Pietroni MA**. Occult pneumonia: an unusual but perilous entity presenting with severe malnutrition and dehydrating diarrhoea. J Health Popul Nutr. 2009 Dec;27: 808-12.

4. Huq S, **Pietroni MA**, Rahman H, Alam MT. Hereditary spherocytosis. J Health Popul Nutr. 2010;28: 107-9.
5. Mazumder RN, **Pietroni MA**, Mosabbir N, Salam MA. Typhus fever: an overlooked diagnosis. J Health Popul Nutr. 2009;27: 419-21.

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.

(Note: Biography of the external Investigators may, however, be submitted in the format as convenient to them)

1 Name: Jonathan Harvey Smith

2 Present Position: Consultant, ICU, Dhaka Hospital, ICDDR,B

3 Educational background:

(last degree and diploma & training relevant to the present research proposal)

B.Sc (Hons). MB BS. FRCA.
Consultant Physician, Special Care Unit, ICDDR,B.
Consultant Paediatric Anaesthetist, Department ofAnaesthesia, Great Ormond Street Hospital, London, UK.
Honorary Senior Lecturer, Portex Unit: PaediatricAnaesthesia, UCL Institute of Child Health, London, UK.
Dr Jonathan Smith BSc. MB. BS. FRCA
Consultant Physician
Special Care Unit
ICDDR,B
68, Shaheed Tajuddin Ahmed Sarani, Mohakhali
Dhaka 1212, Bangladesh

4.0 List of ongoing research protocols

(start and end dates; and percentage of time)

4.5. As Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

4.6. As Co-Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

4.7. As Co-Investigator

Protocol Number	Starting date	End date	Percentage of time

5 Publications

Types of publications	Numbers
g. Original scientific papers in peer-review journals	
h. Peer reviewed articles and book chapters	
i. Papers in conference proceedings	
j. Letters, editorials, annotations, and abstracts in peer-reviewed journals	
k. Working papers	
l. Monographs	

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

1)

2)

3)

4)

5)

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.

(Note: Biography of the external Investigators may, however, be submitted in the format as convenient to them)

1 Name: Tahmeed Ahmed

2 Present Position: **Scientist and Head of Nutrition Programme, ICDDR,B**

3 Educational background:

(last degree and diploma & training relevant to the present research proposal)

MBBS; PhD

4.0 List of ongoing research protocols

(start and end dates; and percentage of time)

4.8. As Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

4.9. As Co-Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

4.10. As Co-Investigator

Protocol Number	Starting date	End date	Percentage of time

5 Publications

Types of publications	Numbers
m. Original scientific papers in peer-review journals	
n. Peer reviewed articles and book chapters	
o. Papers in conference proceedings	
p. Letters, editorials, annotations, and abstracts in peer-reviewed journals	
q. Working papers	
r. Monographs	

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

1)
2)
3)
4)
5)

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.

(Note: Biography of the external Investigators may, however, be submitted in the format as convenient to them)

1 Name: Hasan Ashraf

2 Present Position: Scientist, CSD, ICDDR,B

3 Educational background:

(last degree and diploma & training relevant to the present research proposal)

MBBS; MCPS, MD

4.0 List of ongoing research protocols

(start and end dates; and percentage of time)

4.11. As Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

4.12. As Co-Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

4.13. As Co-Investigator

Protocol Number	Starting date	End date	Percentage of time

5 Publications

Types of publications	Numbers
s. Original scientific papers in peer-review journals	
t. Peer reviewed articles and book chapters	
u. Papers in conference proceedings	
v. Letters, editorials, annotations, and abstracts in peer-reviewed journals	
w. Working papers	
x. Monographs	

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

1. **Ashraf H**, Mahmud R, Alam NH, Jahan SA, Kamal SM, Haque F, Salam MA, Gyr N. Randomized controlled trial of day care versus hospital care of severe pneumonia in Bangladesh. Pediatr 2010;126:e807-15.
2. **Ashraf H**, Alam NH, Rotherermundt C, Brooks WA, Bardhan PK, Hossain L, Salam MA, Hassan MS, Beglinger C, Gyr N. Prevalence and risk factors of hepatitis B and C virus infections in an impoverished urban community in Dhaka, Bangladesh. BMC Infect Dis 2010;10:208.
3. **Ashraf H**, Jahan SA, Alam NH, Mahmud R, Kamal SM, Salam MA, Gyr N. Day-care management of severe and very severe pneumonia, without associated co-morbidities such as severe malnutrition, in an urban health clinic in Dhaka, Bangladesh. Arch Dis Child 2008;93:490-4.
4. **Ashraf H**, Beltinger J, Alam NH, Bardhan PK, Faruque ASG, Akter J, Salam MA, Gyr N. Evaluation of faecal occult blood test and lactoferrin latex agglutination test in screening hospitalized patients for diagnosing inflammatory and non-inflammatory diarrhoea in Dhaka, Bangladesh. Digestion 2007;76;256-261.
5. **Ashraf H,** Ahmed T, Hossain MI, Alam NH, Mahmud R, Kamal SM, Salam MA, Fuchs GJ. Day-care management of children with severe malnutrition in an urban health clinic in Dhaka, Bangladesh. J Trop Pediatr 2007;53:171-8.

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.

(Note: Biography of the external Investigators may, however, be submitted in the format as convenient to them)

1 Name: Sharifuzzaman

2 Present Position: Medical Officer, EDD, CSD

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

MBBS; FCPS (1st part)

4.0 List of ongoing research protocols

(start and end dates; and percentage of time)

a. As Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

b. As Co-Principal Investigator

Protocol Number	Starting date	End date	Percentage of time

c. As Co-Investigator

Protocol Number	Starting date	End date	Percentage of time

5 Publications

Types of publications	Numbers
y. Original scientific papers in peer-review journals	
z. Peer reviewed articles and book chapters	
aa. Papers in conference proceedings	
bb. Letters, editorials, annotations, and abstracts in peer-reviewed journals	
cc. Working papers	
dd. Monographs	

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

1. M. J. Chisti, M. A. Salam, P. K. Bardhan, **Sharifuzzaman**, R. Ahad, S. La Vincente and T. Duke. Influences of dehydration on clinical features of radiological pneumonia in children attending an urban diarrhoea treatment centre in Bangladesh. *Annals of Tropical Paediatrics* 2010; 30: 311-316

2. Mohammod J. Chisti, Mohammed A. Salam, **Sharifuzzaman**, and Mark A.C. Pietroni. Occult Pneumonia: An Unusual but Perilous Entity Presenting with Severe Malnutrition and Dehydrating Diarrhoea. *Journal of Health, Population and Nutrition* 2009; 27: 808-812

3. Mohammod Jobayer Chisti, Pradip Kumar Bardhan, Sayeeda Huq, Wasif Ali Khan, Ali Miraz Khan, **Sharifuzzaman,** and Mohammed Abdus Salam. High-dose intravenous dexamethasone in the management of diarrheal patients with enteric fever and encephalopathy. *Southeast Asian Journal Tropical Medicine and Public Health* 2009; 40: 1065-73

Budget Justifications

Please provide one page statement justifying the budgeted amount for each major item, including the use of human resources, major equipment, and laboratory services.

1. The equipment costs reflect actual costs of only the necessary supplies required for the tests.
2. Personnel costs reflect the actual cost.
3. No laboratory costs (would be done from the hospital costs)

Other Support

Describe sources, amount, duration, and grant number of all other research funding currently granted to PI or under consideration.

My supervisors (Trevor Duke and Steve Graham) from the Royal Children's Hospital, the University of Melbourne has arrange AUS$ 20,000 from AusAID and already sent to ICDDR,B account in favour of this protocol

icddr,b
KNOWLEDGE FOR GLOBAL LIFESAVING SOLUTIONS

Check-List

CHECK-LIST FOR SUBMISSION OF RESEARCH PROTOCOL FOR CONSIDERATION OF RESEARCH REVIEW COMMITTEE (RRC)

[Please check (X) appropriate box]

1. Has the proposal been reviewed, discussed and cleared at the Division level?

   Yes ☒ No ☐

   If No, please clarify the reasons:

2. Has the proposal been peer-reviewed externally [Review has been done several times by external collaborators (Trevor Duke and Stephen M Graham) from the Royal Children`s Hospital, Melbourne]?

   Yes ☒ No ☐

   If the answer is 'No', please explain the reasons:

   If yes, have the external reviews' comments and their responses been attached

   Yes ☐ No ☒

3. Has the budget been cleared by Finance Department?

   Yes ☒ No ☐

   If the answer is 'No', reasons thereof be indicated:

4. Does the study involve any procedure employing hazardous materials, or equipments?

   Yes ☒ No ☐

   If 'Yes', fill the necessary form.

5. Has the Ethics Certificate(s) been attached with the Protocol?

   Yes ☐ No ☒

   If the answer is 'No', please explain the reasons: Yet not faced the ERC

_____ _____

Signature of the Principal Investigator Date

icddr,b
KNOWLEDGE FOR GLOBAL LIFESAVING SOLUTIONS

INFORMATION TO INCLUDE IN ABSTRACT SUMMARY

The Ethical Review Committee will not consider any application that does not include an abstract summary. The abstract should summarise the purpose of the study, the methods and procedures to be used, by addressing each of the following items. If an item is not applicable, please note accordingly:

1. Describe the requirements for a study population and explain the rationale for using in this special population groups such as children, or groups whose ability to give voluntary informed consents might be compromised.
2. Describe and assess any potential risks – physical, psychological, social, legal or other, and assess their likelihood and seriousness. If research methods are anticipated to create potential risks, describe alternate methods, if any, which were considered and why they will not be used.
3. Describe procedures for protecting against or minimizing potential risks and an assessment of their likely effectiveness.
4. Include a description of the methods for safeguarding confidentiality and protecting anonymity.
5. When there are potential risks to the subject, or the privacy of the individual may be affected, the investigators are required to obtain a signed informed consent from the prospective participant.For minors and individuals with compromised ability to provide a valid consent, informed consent must be obtained from their parents or legal guardians. Describe consent procedures to be followed including how and where informed consent will be obtained.
    a) If signed consent will not be obtained, explain why this requirement should be waived and provide an alternative procedure that would be used.
    b) If information is to be withheld from a subject, provide justification for this course of action.
    c) If there is a potential risk to the participant or privacy of the individual might be affected while applying any particular procedure include a statement in the consent form to clarify whether or not compensation and/or treatment will be available.
6. If study involves an interview, describe the place and processes, and state the approximate length of the interview.
7. Assess the potential benefits to be gained or risk the individual participants might be subjected to, and also the benefits that might accrue to the society in general as a result of the planned work. Clarify if and how the benefits outweigh the risks.
8. State if the activity requires the use of records (hospital, medical, birth, death or other), organs, tissues, body fluids, the foetus or the abortus.

    The statement to the potential participants should include information specified in item 2,3,4,5(c) and 7, and also indicate the approximate time they would be required to remain in the activity.

References

1. Koyamaibole L, Kado J, Qovu JD, Colquhoun S, Duke T. An evaluation of bubble-CPAP in a neonatal unit in a developing country: effective respiratory support that can be applied by nurses. J Trop Pediatr. 2006 Aug;52(4):249-53.
2. Gittermann MK, Fusch C, Gittermann AR, Regazzoni BM, Moessinger AC. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. Eur J Pediatr. 1997 May;156(5):384-8.
3. Upadhyay A, Deorari AK. Continuous positive airway pressure - a gentler approach to ventilation. Indian Pediatr. 2004 May;41(5):459-69.
4. McKiernan C, Chua LC, Visintainer PF, Allen H. High flow nasal cannulae therapy in infants with bronchiolitis. J Pediatr. Apr;156(4):634-8.
5. Chisti MJ, Tebruegge M, La Vincente S, Graham SM, Duke T. Pneumonia in severely malnourished children in developing countries - mortality risk, aetiology and validity of WHO clinical signs: a systematic review. Trop Med Int Health. 2009 Oct;14(10):1173-89.
6. Chisti MJ, Ahmed T, Faruque AS, Abdus Salam M. Clinical and laboratory features of radiologic pneumonia in severely malnourished infants attending an urban diarrhea treatment center in Bangladesh. Pediatr Infect Dis J. 2010 Feb;29(2):174-7.
7. Scott JA, Brooks WA, Peiris JS, Holtzman D, Mulholland EK. Pneumonia research to reduce childhood mortality in the developing world. J Clin Invest. 2008 Apr;118(4):1291-300.
8. Ahmed T, Ali M, Ullah MM, Choudhury IA, Haque ME, Salam MA, et al. Mortality in severely malnourished children with diarrhoea and use of a standardised management protocol. Lancet. 1999 Jun 5;353(9168):1919-22.
9. Essouri S, Chevret L, Durand P, Haas V, Fauroux B, Devictor D. Noninvasive positive pressure ventilation: five years of experience in a pediatric intensive care unit. Pediatr Crit Care Med. 2006 Jul;7(4):329-34.
10. Duke T, Blaschke AJ, Sialis S, Bonkowsky JL. Hypoxaemia in acute respiratory and non-respiratory illnesses in neonates and children in a developing country. Arch Dis Child. 2002 Feb;86(2):108-12.
11. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. Jun 5;375(9730):1969-87.
12. Rajaratnam JK, Marcus JR, Flaxman AD, Wang H, Levin-Rector A, Dwyer L, et al. Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970-2010: a systematic analysis of progress towards Millennium Development Goal 4. Lancet. Jun 5;375(9730):1988-2008.
13. Tarnow-Mordi WO, Darlow B, Doyle L. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. Sep 23;363(13):1285; author reply -6.
14. Polin RA. Assisted ventilation of the newborn. Semin Neonatol. 2002;7(5):379 –89

15. Chidini G, Calderini E, Cesana BM, Gandini C, Prandi E, Pelosi P. Noninvasive continuous positive airway pressure in acute respiratory failure: helmet versus facial mask. Pediatrics. 2010 Aug;126(2):e330-6.