# Protocol for Optimisation of Neonatal Ventilation: Determining the appropriate level of volume guarantee for infants with evolving bronchopulmonary dysplasia

*A randomised cross over study assessing the work of breathing when using different volumes (sizes) of mechanical breaths delivered during volume targeted ventilation in preterm infants with evolving bronchopulmonary dysplasia.*

## Sponsor

Sponsoring Organisation/s: King's College London and King's College Hospital NHS
Name of Sponsor Representative: Keith Brennan, Director of Research Management & Director of Administration (Health Schools)
Address: Room 1.8 Hodgkin Building, Guy's Campus, King's College London, LONDON, SE1 4UL.
Tel: 020 7848 6960
Email: keith.brennan@kcl.ac.uk

## Chief Investigator

Name: Professor Anne Greenough
Address: 4th Floor Golden Jubilee Wing, King's College Hospital, Denmark Hill, SE5 9RS
Tel: 020 3299 3037
Email: anne.greenough@kcl.ac.uk

## Name and address of Investigator(s)

Name: Ingran Lingam
Address: 4th Floor Golden Jubilee Wing, King's College Hospital, Denmark Hill, SE5 9RS
Tel: 020 3299 4564
Email: ingran@gmail.com

## Statistician

Name: Professor Anne Greenough
Address: 4th Floor Golden Jubilee Wing, King's College Hospital, Denmark Hill, SE5 9RS
Tel: 020 3299 3037
Email: anne.greenough@kcl.ac.uk

**Study Synopsis**

| | |
|---|---|
| Title | **Protocol for Optimisation of Neonatal Ventilation: Determining the appropriate level of volume guarantee for infants with evolving bronchopulmonary dysplasia** (ONV 3.0 16/08/2016) |
| Protocol Short Title/Acronym | Optimising Neonatal Ventilation |
| Protocol Version number and Date | ONV 3.0 16/08/2016 |
| Study Phase if not mentioned in title | |
| Is the study a Pilot? | Yes |
| Study Duration | 18 months |
| Methodology | Open randomised crossover study . |
| Sponsor name | Mr Keith Brennan |
| Chief Investigator | Professor Anne Greenough |
| REC number | |
| Medical condition or disease under investigation | Evolving Bronchopulmonary Dysplasia |
| Purpose of clinical trial | Evaluation of optimum volumes used in volume targeted ventilation |
| Primary objective | To determine the optimum volume (size) of the mechanical inflation delivered during volume targeted ventilation in babies who remain dependent on respiratory support one week after birth. |
| Secondary objective (s) | To inform a randomized trial comparing volume targeted ventilation to proportional assist ventilation in babies with evolving or established chronic lung disease |
| Number of Subjects/Patients | 18 |
| Trial Design | Randomised cross over |
| Endpoints | Physiological measurements of work of breathing (Pressure time product) |
| Main Inclusion Criteria | Infants born under 32 weeks completed gestational age and ventilator dependent at or beyond one week after birth |
| Statistical Methodology and Analysis | Non-parametric statistics |

## Glossary of Terms and Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| ASR | Annual Safety Report |
| CA | Competent Authority |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| DMC | Data Monitoring Committee |
| EC | European Commission |
| GAfREC | Governance Arrangements for NHS Research Ethics Committees |
| ICF | Informed Consent Form |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| MA | Marketing Authorisation |
| MS | Member State |
| Main REC | Main Research Ethics Committee |
| NHS R&D | National Health Service Research & Development |
| PI | Principle Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| Participant | An individual who takes part in a clinical trial |
| RCT | Randomised Controlled Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SDV | Source Document Verification |
| SOP | Standard Operating Procedure |
| SSA | Site Specific Assessment |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |

# 1. Introduction

Two percent of all babies are born very prematurely and require breathing support in the neonatal period. The survival of ventilated neonates has improved over the last thirty years, such that more than 90% survive the newborn period. Unfortunately, there remains a high incidence of complications. In particular, up to 50% develop a chronic lung disease called bronchopulmonary dysplasia (BPD). This condition is associated with significant morbidity, including prolonged oxygen dependency at home and frequent hospital readmissions.

Volume targeted ventilation is a relatively new modality of ventilation, delivering a constant volume of air regardless of changes in the infant's lung function. We have already demonstrated that both in the acute and weaning phase of respiratory distress in prematurely born infants and in term born infants, larger rather than smaller volumes from the ventilator reduces the work of breathing. Similarly, others have shown in similar populations that higher rather than lower levels reduce the levels of lung inflammation.

There is a growing population of infants with evolving or established chronic lung disease (BPD) who remain ventilator dependent at one week of age. These infants tend to have narrower airways and less lung area available for oxygen uptake, and, therefore, may require larger breaths delivered by the ventilator than infants with acute lung problems, where lung damage has not occurred. Thus results from infants who have acute lung disease or are being weaned from respiratory support cannot be extrapolated to those with evolving or established chronic lung disease (BPD). Hence our aim is to determine the optimum volume targeted level during VTV in infants with evolving or established BPD.

## 2 Trial Objectives, Design and Statistics

### 2.1. Trial Objectives

To determine the optimum volume (size) of the mechanical inflation delivered during volume targeted ventilation in babies who remain dependent on respiratory support one week after birth.

To inform a randomized trial comparing volume targeted ventilation to proportional assist ventilation in babies with evolving or established chronic lung disease.

### 2.2 Trial Design & Flowchart

This is a randomised crossover trial assessing the work of breathing using physiological measurements in infants born prior to 32 weeks of gestational age who remain ventilator dependent beyond one week of age. These measurements (described below) are taken while the infant is receiving conventional pressure limited ventilation (baseline) and then measured during each 20-min period of VTV with breath volumes of 4, 5, 6 and 7 ml/kg delivered in a random order. This allows each infant to be used as their own control, minimising the impact of any underlying confounding factors.

Physiological measurements are performed at the bedside while the infants receive their ongoing care and are fully monitored. The measurements have been used extensively and are well tolerated. Measurements will be only carried out if the infant is clinically stable with normal

levels of respiratory gases (oxygen and carbon dioxide). A small tube (of the same size as a feeding tube) will be passed into the infant's stomach via the nose, containing sensors that allow measurement of pressure above and below the diaphragm generated during breathing. The difference between the values from the two sensors allows calculation of the pressure generated by the diaphragm muscle (pressure-time product of the diaphragm or PTPdi). A flow sensor will be placed between the endotracheal tube and ventilator manifold and the flow signal integrated to volume. The results of these measurements are used in assessments of the work of breathing (WOB). The total duration of measurements will be no longer than three hours, at which point the pressure measurement tube and flow sensor will be removed and no further requests will be made of the baby or their family. The optimal VTV level will be used to subsequently support the baby.

## 2.3 Trial Flowchart

| | | | | | |
|---|---|---|---|---|---|
| Patient information and informed consent | | | | | |
| Physical examination | | | | | |
| | Baseline | Volume 1 | Volume 2 | Volume 3 | Volume 4 |
| Set Volume (4/5/6/7 ml/kg) | X | | | | |
| PTPdi | | | | | |
| Adverse events | | | | | |

## 2.4 Trial Statistics

We have calculated that recruitment of 18 infants allows detection of a difference in the results of the work of breathing between the various volume targeting levels equivalent to one standard deviation in the results with 80% power and 5% significance. We will use non parametric statistics to assess whether differences between volume targeted levels are statistically significant.

## 3. Sample Size, Selection and Withdrawal of Subjects

Power calculation as stated in 2.4 requires the recruitment of 18 infants to participate in the study.

Inclusion Criteria

- Infants born at less than 32 weeks completed gestation who remain ventilator dependent one week after birth.

Exclusion Criteria

- Infants born above 32 weeks of gestational age
- Infants who have been successfully extubated by one week of age
- Complex congenital cardiac abnormalities
- Congenital diaphragmatic hernia

Criteria for Premature Withdrawal

- Parental Request

## 4. Study procedures

### Informed Consent Procedures

Participants will be identified from the daily admission list and parents will be approached by a member of the clinical research team. We will provide them with verbal and written information, allowing at least 24 hours for consideration prior to entry into study.

The clinical fellow will provide a full explanation of the study to the parents. They will highlight that the parents may choose not to allow their infant to be entered into the study and withdraw their child from the study at any time without compromising the child's care.

As the study involves hospital in-patients, consent will also be obtained from the consultant of the patient.

### 4.1 Screening Procedures

There are no study specific screening procedures prior to entry into the study. Eligible infants will be examined by the clinical fellow prior to undertaking physiological measurements in order to ensure they are in a stable condition.

### 4.2 Randomisation Procedures

The order of the set volumes provided to each infant will be randomised prior to undertaking the physiological measurements. This will be performed using Microsoft Excel to generate the random order in which the four volumes to be applied.

### 4.3 Schedule of Treatment for each visit

The initial visit with the parents/carers of eligible infants will be primarily to provide information regarding the study, with a follow up meeting at least 24 hours later to ensure they have sufficient time to process the information and provide informed consent.

The physiological measurements of each study participant will be performed on a single occasion, lasting approximately 3 hours. It is unlikely that repeat study measurements will need to be taken and if required, the reasons will be explained to parents prior to taking place.

### 4.4 Follow up Procedures

There are no specific study procedures for follow up of the participating infants. However, the results of the study will be communicated to the parents following analysis with an explanation on its implications for their infant's future care.

### 4.5 Radiology Assessments *(not applicable)*

### 4.6 End of Study Definition

Following completion of the physiological measurements and analysis of the results of the required number of infants, the REC will be informed that the study has been completed.

## 5. Laboratories (not applicable)

## 6. Assessment of Safety

All measurements are carried out whilst the patient is ventilated and closely monitored as part of routine clinical care. There have been no adverse effects or additional discomfort associated with previous studies which have used the same physiological assessments and similar study design. Infants will be fully examined to ensure clinical stability prior to undertaking measurements.

### 6.1 Ethics Reporting

Reports of related and unexpected serious adverse events will be submitted to the Main REC within 15 days of the chief investigator becoming aware of the event, using the NRES template. The parents will be informed of any events as soon as possible and be provided with an opportunity to meet with clinical and research team. The results of any reports or investigations relating to the events will also be communicated to the parents in writing.

## 7. Trial Steering Committee (not applicable)

## 8. Ethics & Regulatory Approvals

*State the name and address of the REC to which the study protocol and other documentation will be submitted.*

## 9. Data Handling

### Confidentiality

Analysis of the data will take place at King's College Hospital and is to be undertaken by a clinical research fellow and by Professor Greenough, the principle investigator.

Each patient will be assigned a unique patient identifier, under which patient data will be anonymously stored on a password protected computer. All paper copies containing patient identifiable data will be kept in a locked filing cabinet until the patients are 16 years of age. Only the principal investigator and research fellow involved in the study will have access to the data, the principal investigator will act as custodian

### Case Report Form

Elements included in each case report form (CRF):
-Unique patient identifier
-Date of parental consent
-Eligibility criteria checklist
-Date of measurements
-Record of clinical examination
-Study template documenting the order of volume targets as per randomisation and PTPdi results
-Any adverse events noted during measurements

Completion of the CRF will be the responsibility of the clinical research fellow.

**Record Retention and Archiving**
Records will be held in a locked filing cabinet located within the research office based at the neonatal unit of Kings College Hospital. Access is limited to the clinical research fellow and Chief Investigator.

**Compliance**
The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

**Clinical Governance Issues**

**-Audit and Inspection**
Accurate records of all research activity including copies of the consent forms and completed case report forms will be safely stored and audited for compliance if requested.

**-Non-Compliance**

The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

## 10. Finance and Publication Policy

Consumables for this study have been funded by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. As a clinical trainee, the salary of the research fellow undertaking this study is provided by the London Deanery.

**Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research**

| | Who | When | How | To Whom |
|---|---|---|---|---|
| **SAE** | Chief Investigator | -Report to Sponsor within 24 hours of learning of the event<br><br>-Report to the MREC within 15 days of learning of the event | SAE Report form for Non-CTIMPs, available from NRES website. | Sponsor and MREC |
| **Urgent Safety Measures** | Chief Investigator | Contact the Sponsor and MREC Immediately<br><br>Within 3 days | By phone<br><br>Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action. | Main REC and Sponsor<br><br>Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt. |
| **Progress Reports** | Chief Investigator | Annually ( starting 12 months after the date of favourable opinion) | Annual Progress Report Form (non-CTIMPs) available from the NRES website | Main REC |
| **Declaration of the conclusion or early termination of the study** | Chief Investigator | Within 90 days (conclusion)<br><br>Within 15 days (early termination)<br><br>*The end of study should be defined in the protocol* | End of Study Declaration form available from the NRES website | Main REC with a copy to be sent to the sponsor |
| **Summary of final Report** | Chief Investigator | Within one year of conclusion of the Research | No Standard Format However, the following Information should be included:-<br>Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants | Main REC with a copy to be sent to the sponsor |