Trial Protocol

Optimising mechanical ventilation in newborns using capnography

Sponsor:	King's College Hospital NHS Foundation Trust (KCH) and King's College London (KCL)
Funder (s):	Charles Wolfson Charitable Trust SLE Ltd
IRAS Reference	248018
ISRCTN / Clinicaltrials.gov no:	[Insert ISRCTN or Clinicaltrials.gov reference no]

Protocol Version 1.0 06/08/2018

KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the R&I Office of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

PRINCIPAL INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

CLINICAL RESEARCH FELLOW: The clinical research fellow will be responsible for recruiting participants, making study measurements, and collecting and analysing relevant data as per the study protocol.

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information Governance policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of this research without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature:..... Date...../...../.....

Print Name(in full):.....

Position:.....

Contents

List of abbreviations

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	Human Tissue Authority
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

1 Trial personnel

Chief Investigator	Professor Anne Greenough e-mail: anne.greenough@kcl.ac.uk tel: 02032999000 ex 3037
Sponsor	R&I Manager, King's College Hospital NHSFT 161 Denmark Hill, London, SE5 9RS and Director of Research Management and Innovation, King's College London, Room 5.23, James Clerk Maxwell Building, Waterloo Campus, 57 Waterloo Road, London SE1 8WA

2 Summary

STUDY OVERVIEW	
Full title	Optimising mechanical ventilation in newborns using capnography
Objectives	Summarise primary and secondary objectives.
Type of trial	Cohort study of mechanically ventilated neonates
Trial design and methods	Give brief summary of trial design and the assessments that will be made to achieve the primary and secondary objectives.
Health condition(s) or problem(s) studied	
Target sample size	200 (plus 200 historical controls)
Trial design and methods	Cohort study. Included infants will receive sidestream capnography monitoring in addition to routine care. The frequency of complications of mechanical ventilation and the number of blood gases required will be compared to historical controls. The data will also be analysed to assess dead space in infants with differing neonatal respiratory diseases and the sidestream capnography measurement will be validated against arterial CO_2 measurement and mainstream capnography.
Trial duration per participant:	From consent until no longer invasively mechanically ventilated
Main inclusion/exclusion criteria:	Infants who are mechanically ventilated on the NICU will be eligible for inclusion
Statistical methodology and analysis:	Data will be assessed for normality and non-parametric and parametric statistics used as appropriate to compare outcomes.
STUDY TIMELINES	
Study Duration/length	2 years
Expected Start Date	1/10/2018
End of Study definition and anticipated date	31/8/2020, once recruitment completed and data analysed.
Key Study milestones	

3 Background and Rationale

Seven percent of all infants are born prematurely and many require respiratory support in the newborn period. Mechanical ventilation can be life-saving, but unfortunately is associated with long term complications. The most common adverse outcome of premature birth is chronic respiratory morbidity including bronchopulmonary dysplasia (BPD). Prematurely born infants may also suffer intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL) which result in adverse neurodevelopmental outcome at follow-up, including cerebral palsy. Those complications are increased in infants who have suffered abnormalities in carbon dioxide (CO2) levels and indeed such abnormalities can also result in adverse neurodevelopmental outcomes in infants born at term. It is thus essential, if the outcomes of infants requiring respiratory support in the newborn period are to be improved, carbon dioxide levels are more appropriately monitored.

Unfortunately, a number of methodological limitations, relating to the anatomical and physiological characteristics of infants, have so far precluded the use of tidal capnography in neonatal intensive care. Such characteristics are their high respiratory rates, the very small flows and volumes generated by newborn infants and the relatively high dead space of the capnographs in relation to the tidal volume of premature infants [18]. For example, a premature infant of 500 grams has a tidal volume of 2.5 mls, while previously-used capnographs had an instrumental dead space of 2.8 mls [19]. The addition of such a dead space would lead to calculation of an inappropriately low dead space leading to inaccurate recommendations regarding clinical management such as the readiness for extubation and the administration of an insufficient targeted tidal volume. Most importantly, a high dead space mainstream capnograph would increase the infant's CO2 level by the addition of the apparatus dead space. Not surprisingly then, mainstream ETCO2 monitoring has been demonstrated in very low birth weight infants to correlate poorly with PaCO2 levels and be negatively influenced by the severity of pulmonary disease [20]. We have, however, recently described use of a low-dead space mainstream capnograph to accurately calculate anatomical and alveolar dead space even in extremely premature infants [21]. The anatomical dead space (the conducting non-gas exchanging

units) and the alveolar dead space (which is the ventilated alveoli that are not perfused) together make up the physiological dead space. Furthermore, we have also shown that dead space results obtained prior to extubation accurately predicted the development of later severe respiratory complications: BPD and need for supplemental home oxygen at discharge from neonatal care [22]. Those results suggest routine assessment of dead space would identify infants at high risk of complications and hence in need of preventative management. The dead space of common neonatal respiratory conditions, for example respiratory distress syndrome (RDS), evolving BPD, meconium aspiration syndrome (MAS) and persistent pulmonary hypertension of the newborn (PPHN) in ventilated infants, however, is not known. Hence, an aim of this application is to provide such information which is essential to reduce the complications of invasive mechanical ventilation related to abnormal carbon dioxide levels.

Side stream capnography

The problems of main stream capnography are avoided by use side stream capnography, but this technique has been problematic in premature infants. The previously used sampling rates of gas represented a significant fraction of the infant's minute ventilation and resulted in inaccurate results [18]. Technological advances have resulted in very low sampling rate, side stream capnography (50ml/min rather than 150-200 ml/min). In a small sample of healthy new-borns (n=7), results from such a capnograph were shown to accurately reflect alveolar CO2 levels [23]. Recent further advances have allowed the integration of very low sampling rate side stream tidal capnography into ventilator software and real time, continuous demonstration of CO2 end-tidal values. A further aim of this application is then to determine the validity of this technique in comparison to low sampling main stream capnography against arterial CO2 results. We hypothesise that using such a technique to provide continuous monitoring will reduce the time spent with abnormal CO2 levels and the occurrence of related complications. Indeed, using an invasive technique which sampled breath close to the carina significantly reduced the time spent with unsafe CO2 levels and the incidences of IVH and PVL [24]. Unfortunately, a double lumen endotracheal tube was required to improve the

accuracy of the technique and such endotracheal tubes are not used in routine clinical practice. In contrast, validated ventilator incorporated low sampling rate, side-stream capnography could be used in routine practice. We will determine whether the results of the novel technique of low sampling rate, side-stream capnography incorporated in ventilator software will correlate with the results of low dead space mainstream capnography and arterial blood gas CO2 measurements. In the proposed research, we will investigate whether real time, continuous capnography (non-invasive assessment of CO2 levels) will allow earlier detection of acute complications in mechanically ventilated infants, such as a blocked or dislodged endotracheal tube or a pneumothorax and reduce the average daily frequency of invasive blood sampling which results in anaemia and hence associated complications related to blood transfusions. We also aim to accurately calculate the anatomical and alveolar dead space in infants with various neonatal respiratory diseases using real time monitoring by capnography and hence appropriate tidal volumes will be delivered. Reducing the delivery of inappropriately high or low tidal volumes, we hypothesise will reduce the development of serious complications such as BPD, IVH and PVL.

4 Objectives

Primary:
To assess whether sidestream capnography reduces the frequency of complications and blood gas sampling in mechanically ventilated infants on the neonatal unit.

Secondary:
To validate sidestream capnography sampling against mainstream capnography sampling and arterial carbon dioxide measurement.
To use sidestream capnography in the assessment of dead space measurements in infants with neonatal respiratory diseases
To

5 Trial design

Cohort study of novel intervention (micro-sidestream capnography) compared against historical control group.

6 Selection of Participants

6.1 Inclusion criteria

1. Infants cared for on NICU who are mechanically ventilated
2. Written informed consent obtained from parents

6.2 Exclusion criteria

1. Lack of informed consent
2. Not mechanically ventilated.

6.3 Recruitment

Parents of potential participants will be first approached by a member of the direct clinical care team (nurse/doctor caring for the patient). If parents indicate that they would like information about the study then they will be approached by a member of the research team who will provide an explanation of the research and a Participant Information Sheet and answer any questions. Parents will be given at least 24 hours to decide if they would like their child to take part in the study.

Participant recruitment at a site will only commence when the trial has:

1. Been confirmed by the Sponsor (or its delegated representative)
2. Received HRA Approval , and
3. Has confirmed Capacity and Capability

6.4 Informed consent

As participants are infants, written informed consent will be sought from their parents/legal guardians.

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.
The person taking consent will be suitably qualified and experienced, and will have been delegated this duty by the CI/ PI on the Delegation Log.

Consent will be sought at least 24 hours after being given the study documentation. It must be recorded in the medical notes (including version and date of the PIS) when the participant information sheet (PIS) has been given to the parents.
The Investigator or designee will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.
No trial procedures will be conducted prior to the participant giving consent by signing the Consent form. Consent will not denote enrolment into trial.

A copy of the signed Informed Consent form will be given to the child's parents. The original signed form will be retained in the trial file at site and a copy placed in the medical notes.
The PIS and consent form will be reviewed and updated if necessary throughout the trial (e.g. where new safety information becomes available) and participants will be re-consented as appropriate.

7 Product/Interventions

7.1 Name and description of intervention(s) under investigation

Sidestream capnograph integrated with ventilation.

8 Trial procedures

8.1 Screening assessments

The following trial specific procedures will be carried out after consent to assess the participant's eligibility:
Observing that child is mechanically ventilated.
All screening procedures will be carried out as specified in the schedule of assessments (appendix 1).

8.2 Registration/Randomisation Procedures (delete as appropriate) (if applicable)

Following participant consent, and confirmation of eligibility (see section 8.1 for screening assessments), the registration/randomisation procedure described below will be carried out.
Participants will be registered with a participant trial number and a sidestream capnograph incorportated into the ventilator circuit. There is no randomisation in this study.
Participants are considered to be enrolled into the trial following: consent, screening assessments (see section 8.1), confirmation of eligibility, completion of the registration/randomisation process, allocation of the participant trial number and intervention.

8.3 Intervention procedures

The sidestram capnograph will be incorporated into the ventilator circuit until the infant is no longer receiving invasive mechanical ventilation.
The intervention will be carried out on the NICU by the clinical research fellow.

8.4 Subsequent assessments and procedures

Data will be collected on the frequency of complications (blocked/dislodged endotracheal tube, pneumothorax, hypo or hypercarbia) and the frequency of blood gas sampling. Results of arterial blood gas sampling performed as part of routine care will be recorded.
For the sub-cohort involved in the validation study, the NM3 mainstream capnograph will also be inserted into the ventilator circuit for a twenty (20) minute period.
A schedule of all trial assessments and procedures is set-out in Appendix 1.

8.6 Discontinuation/withdrawal of participants

In consenting to participate in the trial, participants are consenting to intervention, assessments, follow-up and data collection.
A participant may be withdrawn from trial whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing the trial may include:

- patients withdrawing consent
- withdrawal due to clinician request

The decision to withdraw a participant from treatment will be recorded in the CRF and medical notes. If a participant explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded in the CRF and medical notes.

8.7 Definition of End of Trial

The expected duration of the trial is 2 years from consent of the first participant.

8 Safety Reporting

9.1 Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or trial participant, which does not necessarily have a causal relationship with the intervention involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect. Medical judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.
* A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

9.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

9.2.1 Severity

The generic categories below are given for use as a guide. You may have a more specific scale that you want to use related to the disease (e.g. CTCAE criteria), amend as required.

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further intervention, but is not damaging to health; it causes

	moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

9.2.2 Causality

The assessment of relationship of adverse events to the intervention is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

9.2.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the intervention listed in the manual of operation
Unexpected	An adverse event which is not consistent with the information about the intervention listed in the manual of operation

* This includes listed events that are more frequently reported or more severe than previously reported.

The reference document to be used to assess expectedness against the Intervention is the manual of operation

9.3 Recording adverse events

All adverse events will be recorded in the medical records in the first instance.

All Adverse events will be recorded in the CRF following consent.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

9.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and the CRF, and the sponsor's AE log The AE log of SAEs will be reported to the sponsor at least once or twice per year.

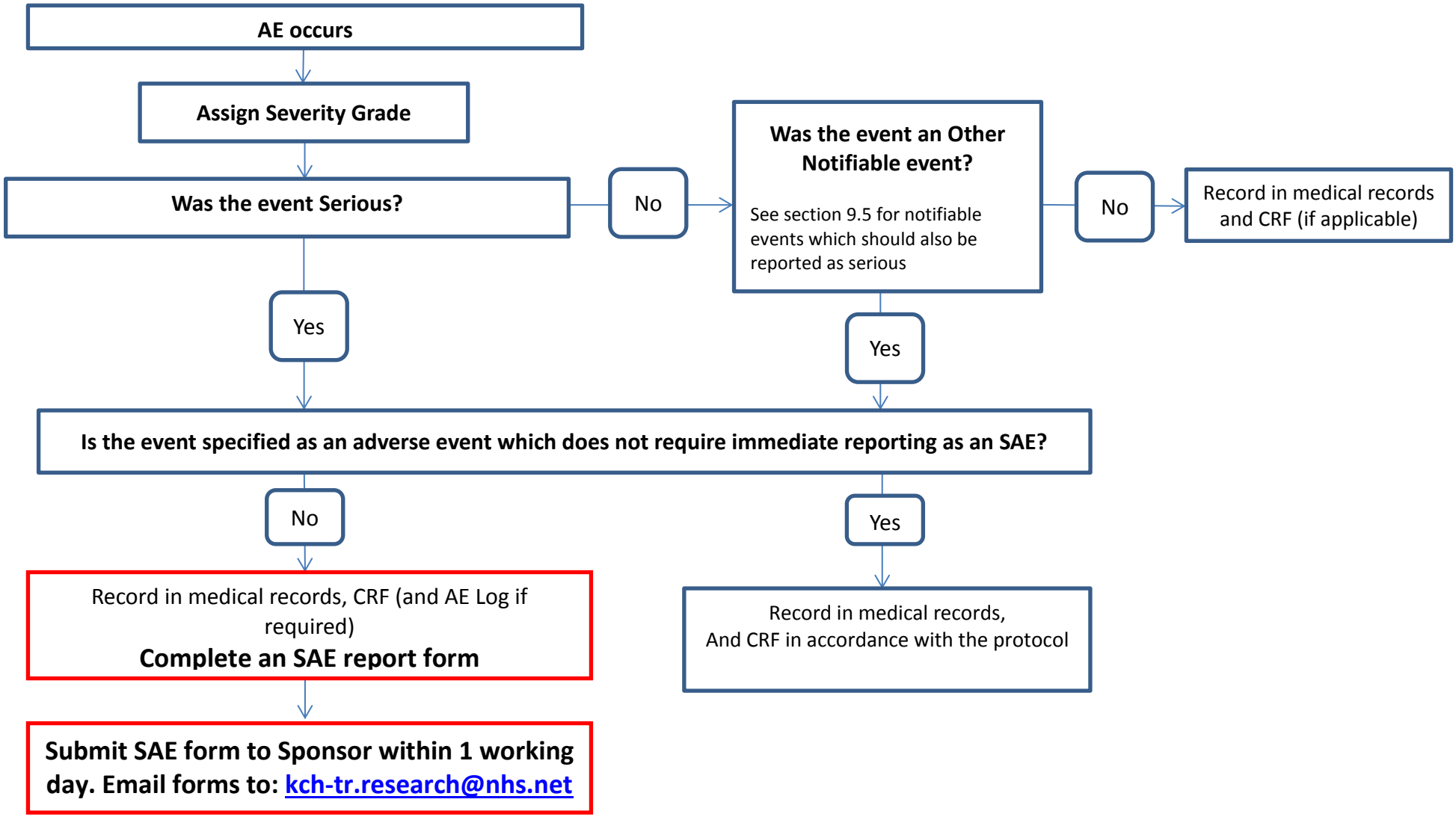
All SAEs (except those specified in section 9.5 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete the sponsor's SAE form and the form will be preferably emailed to the Sponsor within 1 working day of

becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.
Where the event is unexpected and thought to be related to the intervention, this must be reported by the Chief Investigator / Sponsor to the Health Research Authority within 15 days.

Completed SAE forms must be sent within 1 working day of becoming aware of the event to the Sponsor
Email forms to: kch.tr-research@nhs.net

Managing serious adverse events in a multi-site trial (if applicable)
SAEs will be reported to the sponsor until 30 days following last interventional procedure.

Flow Chart for SAE reporting



9.7 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

9.8 Notification of reportable protocol violations

A reportable protocol violation is a breach which is likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial.
The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

9.9 Reporting incidents involving a CE marked medical device(s) (if applicable)

Any adverse incident involving a medical device should be reported to the manufacturer of the device.
This is especially important where the incident has led to or, was it to occur again could lead to an event classified as serious (see section 9.1 for definition of SAE). Other minor safety or quality problems should be reported along with incidents that appear to be caused by human error.
All adverse incidents must be reported to SLE Ltd.
Incidents should be reported as soon as possible (usually within 24 hours).
Adverse incidents related to a medical device can be reported directly to the MHRA via the online system (www.mhra.gov.uk). Alternative contact details: Medicines & Healthcare products Regulatory Agency Adverse Incident Centre (Tel: 020 7084 3080; Fax 020 7084 3109).
Local trust reporting procedures may also need to be followed. It is the responsibility of the PI and trial site team to ensure they are aware of any specific local requirements for reporting device incidents.

9.10 Trust Incidents and Near Misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.
A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

10 Data management

10.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.
The Case Report Forms (CRFs) will not bear the participant's name or other personal identifiable data. The participant's trial identification number will be used for identification and this will be clearly explained to the patient in the Patient information sheet. Patient consent for this will be sought.

10.2 Data collection tools and source document identification

Data will be collected from sites on trial specific case report forms (CRFs) or data collection tools such as electronic CRFs.
Source data are contained in source documents and must be accurately transcribed on to the CRF. Examples of source documents are medical records which include laboratory and other clinical reports etc.
It is the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

10.3 Completing Case Report Forms

All CRFs must be completed and signed by staff that are listed on the delegation log and authorised by the CI/ PI to perform this duty. The CI/PI is responsible for the accuracy of all data reported in the CRF.

10.4 Data handling

In the study, gestational age, birthweight, antenatal steroid exposure, ventilator settings, and current age will be collected from patients in accordance with the patient consent form, patient information sheet and the protocol.

The CI act as the data controller of such data for the study and will process, store and dispose of the above data in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 1998 and any amendments thereto. Data will be stored under a pseudonym in a locked filing cabinet to which only the research team have access.

Capnography data, but no personal identifiable information, recorded from infants will, with parental consent, be transferred to SLE for further assessment and analysis.

11 Statistical Considerations

11.1 Primary Outcome

Frequency of complications of mechanical ventilation (pneumothorax, blocked or dislodged endotracheal tube, hypo or hypercarbia) and of routine blood gas sampling.

11.2 Secondary outcome(s)

Validation of sidestream capnograph against mainstream capnography and arterial CO2 measurement

Anatomical and alveolar dead space measurement in ventilated infants with neonatal respiratory disease.

11.3 Sample size calculation

Based on the unit's activity over the past two years and our highly successful recruitment into research studies, we anticipate that we will prospectively assess at least 200 infants. Such numbers will allow us to draw clinically meaningful conclusions from our proposed studies with at least 80% power at the 5% level of significance to detect differences regarding the incidence of acute complications and frequency of blood sampling.

In a previous study, we found a clinically significant difference in dead space of 0.9 ml/kg between premature infants who developed BPD and premature infants who did not develop BPD [22]. The standard deviation of the anatomical dead space results was shown to be 0.8 ml/kg [21] Thus, twenty-seven subjects in each group will allow detection of a difference in dead space of 0.9 ml/kg between two groups with 90% power at the 5% level. During the last two years, 93 infants born less than 28 weeks of gestation with respiratory distress syndrome, 65 infants with BPD at 28 days, 72 infants with meconium aspiration syndrome and 44 infants with persistent pulmonary hypertension of the newborn have been ventilated on our unit so more than sufficient for us to complete this study in four neonatal respiratory diseases.

For validation against the NM3 mainstream capnograph/arterial CO_2 monitoring we will recruit 40 infants.

The research team will review interim efficacy at six months after commencing the study. This will involve an interim power calculation. We do not anticipate safety issues to arise as part of this study as the study will only be recording physiological measurements obtained during standard clinical care. If the interim power calculation detects that the objectives of the study have either been reached or will be reached before completing the recruitment of our intended sample size, the study will be terminated once the objectives have been reached.

11.4 Planned recruitment rate

Recruitment at a rate of approximately 9-10 infants per month will be required. As a busy tertiary neonatal unit with 12 ITU cots, there will be sufficient numbers of potential participants to enable recruitment to time and target.

11.6 Statistical analysis

11.6.2 Primary outcome analysis

The incidence of acute complications of mechanical ventilation such as atelectasis, blocked, dislodged or kinked endotracheal tube and pneumothorax will be recorded in infants ventilated with continuous tidal capnography. The actions taken to address the complications will be recorded and whether the actions were instituted on the basis of the results of capnography or other adjuncts such as radiography. The incidence of complications in infants with or without capnography monitoring, and frequency of blood gas sampling will be assessed for statistical significance using the Chi square test

11.6.3 Secondary outcome analysis

Calculation of the anatomical and alveolar dead space

The anatomical and alveolar dead space will be calculated by real time, side stream capnography and main-stream capnography in infants with RDS, evolving BPD, MAS and PPHN and the results

compared. The agreement between side stream and mainstream capnography will be tested with correlation analysis and Bland Altman plot construction. Results will be assessed for normality with the Kolmogorov- Smirnoff test. If the ETCO2 data are normally distributed Pearson's correlation analysis will be used and if they are not normally distributed Spearman's rho correlation analysis will be used. Normally distributed variables will be assessed for statistical significance between infants with different underlying pathologies by t test or ANOVA and non-normally distributed variables by the Mann-Whitney U and Kruskall Wallis tests.

Validation of side-stream end-tidal CO2

This will be determined by comparing the results against mainstream CO2 and arterial CO2 levels. The agreements between side stream and mainstream capnography and arterial CO2 levels will be tested with correlation analysis and Bland Altman plot construction. If the ETCO2 data are normally distributed Pearson's correlation analysis will be used and if they are not normally distributed Spearman's rho correlation analysis will be used.

12 Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI for a minimum of 25 years from the declaration of end of trial.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

13 Oversight Committees

13.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator and trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly.

The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC.

14 Ethical requirements and patient and public involvement

14.1 Ethics and Health Research Authority (HRA)

The sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate research ethics committee and HRA, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

Before any NHS site may be opened to recruit participants, the Chief Investigator/Principal Investigator or designee must ensure confirmation of Capacity and Capability has been given by the local R&D office. It is the responsibility of the CI/ PI or designee at each site to ensure that all subsequent amendments gain the necessary approvals. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants (see section 9.6 for reporting urgent safety measures).

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The chief investigator will prepare the APR.
Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.
The CI will supply the Sponsor with a summary report of the trial, which will then be submitted to the REC within 1 year after the end of the trial.

14.2 Patient and public involvement (PPI)

15 Monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.
The degree of monitoring will be proportionate to the risks associated with the trial.
A trial specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan.

16 Finance

The study is funded by the Charles Wolfson Charitable Trust and by SLE (Ltd). SLE have had no input into the design of the study. The CI and co-investigators have no conflicts of interest to declare.

17 Insurance

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&I Office. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the KCH R & I Office.

King's College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that KCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. King's College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

The manufacturer of the sidestream capnograph will provide an indemnity document which is necessary prior to the devices being admitted to use on the NICU.

18 Publication policy

The intention is to publish results of the study in peer-reviewed scientific journals and for presentation at conferences. No identifiable information will be published.

20 Appendices

Appendix 1 - Schedule of assessments

	Screening (Pre-treatment assessment)	Intervention phase		Final visit
Visit No:	1	2	3	8
	-x - 1	Day 1	1-end	At extubation (end of mechanical ventilation)
Informed Consent	X			
Medical History	X			
Insertion of sidestream capnograph into ventilator circuit		X		
Validation against mainstream capnograph (sub-cohort) once for 20 minutes			X	
Eligibility confirmation	X	X		
Adverse Events review	X	X	X	X
Chart review /recording complications/recording frequency of blood gas sampling/recording of arterial blood gas results		X	X	X

Appendix 2 - Protocol Version History

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
1	6/8/18		